SITUS INVERSUS VISCERUM COMPLETUS-
SIGNIFICANCE AND ETIOLOGY

by

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Abbreviations used in text:

CHD	congenital heart disease
EEG	electroencephalogram
EKG	electrocardiogram
L	left
R	right
LLQ	left lower quadrant
RLQ	right lower quadrant
NR	no record
P.X.	physical examination
SIV	situs inversus viscerum
SIVC	situs inversus viscerum completus

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Acknowledgments

Individuals with SIVC whose families are studied in this series, were found and studied with indispensible aid rendered by physicians, social service workers, nurses, technicians, and medical students. With the sympathetic cooperation of members of the McGill Faculty it has been possible to utilize x-ray methods in the demonstration of normality (situs solitus) and abnormality (situs inversus) in all members of the affected families. Thus an objective record is available to make this series particularly reliable. Other members of the Faculty have generously lent their time and certain facilities of the Teaching Hospitals which are under their control, toward making this study as complete and credible as possible. Acknowledgment of the favors extended by North Carolina physicians and members of the staff of Bowman Gray School of Medicine and the North Carolina Baptist Hospital in Winston-Salem, also is gratefully advanced. A debt of gratitude is owed to so many that individual acknowledgments cannot be made here, but all who are participating in this continuing study are assured of the author's appreciation of their invaluable help.

I.

INTRODUCTION

A. Criteria for genetic studies in medicine.

Allergy, which was the original subject for the author's thesis, is not a single nosological entity. For that reason it was abandoned after months of study in 1939-40, in favor of the congenital form of heterotaxy known as situs inversus viscerum (to be defined below), a condition which more nearly approaches the characteristics of a Mendelian unit character.

Jervis (362) gives two requirements for a genetic study (that it may concern itself with a condition fulfilling the Mendelian postulate of a "unit character"): 1) a painstaking clinico-pathological investigation aiming to separate clear-cut nosological entities, and 2) rigorous identification, by means of exact criteria, of the character under study.

Situs inversus viscerum completus (SIVC) fulfills these requirements, as will be demonstrated below (cf. History and Definition).

A further requirement which medical men would put forward, in criticism of much of the work thus far reported in medical genetics, is likewise met in this study. That is the requirement that the character be one of practical importance. Whereas the knowledge of the mode of inheritance of ear-pitting might be of great practical importance to medical geneticists in building a chromosome map, the

recognition of ear-pitting in a sick patient is of no known clinical significance. On the other hand, it is possible to interest practitioners in visceral transposition because recognition of such condition is of the utmost importance in treating patients with a variety of complaints. (Kuchenmeister -- cf. quotation at beginning of Section II.)

B. Asymetry in Biology

Some elementary textbooks of biology consider, briefly at least, the question of symmetry:

"Animals are either symmetrical or asymmetrical. The symmetrical animals may be divided into two types: 1) radially symmetrical, and 2) bilaterally symmetrical. A radially symmetrical animal possesses a number of similar parts, called antimeres, which radiate out from a central axis. The adult starfish is a good example.....Radial symmetry is best suited to sessile animals.....The bodies of bilaterally symmetrical animals are so constructed that the chief organs are arranged in pairs on either side of an axis passing from the head or anterior end to the tail or posterior end. There is only one plane through which their bodies can be divided into two similar parts. An upper or dorsal surface and a lower or ventral surface are recognizable, as well as right and left sides. Bilateral symmetry is characteristic of the most successful animals living at the present time, including all of the vertebrates and most of the invertebrates."

Considerable attention has been paid to deviations from the pattern of so-called bilateral symmetry. One of the most obvious of these deviations is superiority of one hand over the other. Functional inequality of the two sides of the body, although most manifest in the hands, extends to other structures (cf. below under Anatomy and Physiology). A very extensive bibliography on handedness may be found in Wile's book (436), "Handedness". Ludwig has studied the problem in animals as well as man (383). Apparently handed-

ness is an asymmetrical characteristic of numerous animals other than man. Darby (329) has experimented with the mechanism of asymmetry in Alpheidae, producing a reversal or non-reversal of regenerating chelae at will. Isai and Maurer and Peterson (358) have devised tests for handedness in the rat. Friedmann and Davis (339) describe "Left-handedness in parrots".

Dahlberg (328) has discussed the published data on asymmetry in hereditary characters in cats, chickens, rabbits, etc. Gruneberg (399) provides a classification of the causes of asymmetry in animals, giving examples from a wide range of animals.

C. Asymmetry in man.

Besides handedness, the ordinary, so-called normal man manifests asymmetry in numerous ways (some to be described under Anatomy and Physiology). This constitutes asymmetry within normal limits. In seeking an explanation for the constancy of this pattern of normal asymmetry, it is well to look attentively also at more obvious asymmetry, regarded as pathological because of its excess.

Hemimacrosomia # is a term devised to distinguish one pathological form of unilateral asymmetry from normal unilateral asymmetry. It is often accompanied by other stigmata of congenital maldevelopment including telangiectases, syndactylism, mental defect, etc. (the mode of inheritance of some of which stigmata is known). However, no satisfactory explanation for hemiacrosomia in man

synonyms: unilateral hypertrophy, hemihypertrophy, congenital hemihypertrophy, partial gigantism.

has as yet been offered. Gesell (346) considers it an imperfect form of twinning. Autopsy material is not available for most of the (more than 60) cases reported, so that direct comparisons with sexually altered forms (cf. below) in other animals is not feasible. Halperin's review of autopsy material provides one possible clue. The case of Hutchison (356) showed hypertrophy of the R suprarenal gland and the R testis.

Fekete (335) reports a case of lateral hermaphroditism in Mus musculus, the right side (R) revealing an ovary, oviduct and uterine horn; the left side, (L) testis, caput epididymis, vas deferens, seminal vesical, and uterine horn, and the external genitalia of a female. Burril, Greene, and Ivy (319) experimented with the effect of sex hormones on embryonic structures in the rat, discovering that the L Wolffian duct of the female embryo is more sensitive to androgen stimulation than the R. (Note it was the L of Fekete's female mouse that bore the testis.) In the male embryo the R Wolffian duct was more sensitive to inhibitory estrogens and the R gonad was more readily inhibited from normal testicular descent (by exhibition of estrogens). Consequently the L of their rat embryos is considered more masculine and the R more feminine in response to sexual hormone exhibition.

In contrast is the condition in birds where the "female side" appears to be the left. Hens reveal a single left ovary and an atrophied R gonad except in the unusual birds reported by Crew and Munro (325) and others. These are known as gynandromorphs. They are important

to the present discussion inasmuch as they manifest a bilateral size asymmetry of approximately the same degree as that found in human hemimacrosomia (4 - 8%). Gynandromorphism is a "condition in which male characterization is present on one lateral half of the body, female characterization on the other, the individual belonging to a species in which the sexes are normally separate and distinct". (Crew and Munro) Where the bilateral size difference is about 5% they explained their findings by the hypothesis of unilateral autosomal elimination. Where the difference was of the order of 10-15%, the evidence favored a non-disjunction hypothesis. They also concluded that larger size is no real criterion of maleness, and that, furthermore, the size difference is not due to the elimination of an x or y chromosome. The loss of an autosome does not mean necessarily that the side will be smaller, because the recessive chromosome (normally paired with the eliminated autosome) may possess more size genes than the missing dominant allele.

Until further work has been done on hemimacrosomia in man, it is not possible to state definitely whether there is any parallelism between gynandromorphism in fowl and the former. It is also interesting to note the analogy which Ludwig (384) has drawn between sex and asymmetry, which are known to be simultaneously affected in the bird hemihypertrophy, and which may be linked in human hemihypertrophy. Ludwig shows that in each there are two extremes (male and female; right and left). He states that all cells of each (even haploid) are bipotential and that total and partial inversions are possible,

of both genotypic and phenotypic origin, in the two cases. Finally, Ludwig postulates that the developmental process responsible for handedness (physiological or normal size asymmetry) is an exact counterpart of that responsible for sex: three-membered reaction system consisting of genes, activators, and plasma. The direction taken depends which activator gains the upper hand during development.

The available evidence cited above suggests that the L of the mouse and rat is more masculine than the R, and the R of the bird is more masculine than the L. Landauer (375) states that the L of man is more frequently involved in hemihypertrophy than the R, that males are affected more than females, and that the subjects display more L-handedness than the normal population. Gesell (345) found females more frequently affected and stated that 55% of the hypertrophy was right-sided. The pathological condition (man) known as massive hypertrophy of the female breast has been reported in 240 cases (366) and in 25 unilateral cases the hypertrophy occurred 17 times on the L to 8 times on the R. The L breast is normally slightly larger than the R (cf. under Anatomy). There is insufficient evidence to conclude that the normal asymmetry and the pathological asymmetry of man are linked with a normal, sexual, bilateral asymmetry or potential asymmetry. If this evidence became available, the answer to the etiology of normal and pathological asymmetry in man might be sought along the same lines as in fowl, with more assurance of success than at present.

A general rule regarding asymmetry has been given by Snyder (423):"it may be stated that when a trait which

could be bilateral is found in a unilateral condition, it is most probably due to environment; but when it is found in a bilateral condition, it is most probably the result of a genetic change". To show that asymmetry in man does occur on a hereditary basis, examples from Snyder's book (423) may be cited. "As in cancer, tuberculosis tends to attack the same organ, or even the same part, such as the right or left lung, in families." Snyder cites the case of Champlin's twin boys who developed sarcoma of the testis - both on the R. "Other cases of similar cancers in two members of a pair of identical twins are on record: retinal blastoma of the left eye.....ovarian cysts on the same side.....fibro-adenoma of the same quadrant of the left breast." Passow (397) describes sectorial brown pigmentation of an otherwise blue eye, as an inherited trait traceable for 4-5 generations in three families - always keeping to the same side! There is no point in adding further examples to this list. It is enough to know that a genetic basis has been found for some forms of asymmetry (other than SIV).

Crew and Munro (325) found examples of mosaic hypertrophy; Gesell (346) likewise has noted such cases in man - termed partial hypertrophy. The fowl mosaics may be explained (according to Crew and Munro) on a genetic basis. The human partial hypertrophies can, in some cases, be explained on a superficially non-genetic basis. An example from Schwartz and Greene (418) is the case of an eight year old Italian girl with coarctation of the isthmus of the aorta involving the mouth of the left sub-

clavian artery. The R of her face and chest, the R arm circumference and length, were larger than the contralateral features. The arterial pulse in the L subclavian, axillary, brachial, radial, and bilateral abdominal and femoral vessels was markedly diminished or absent. Blood pressure readings were not obtainable in the L arm or the legs. The bilateral size difference was apparently due to bilateral difference in blood supply. Similar cases are reported by other authors. Comparable asymmetry in other cases is attributed to: arteriovenous fistulae, vascular nevi, hemangiomas, lymphangiomas, circulatory changes from cervical ribs.

While study of various types of asymmetry may be of help eventually in understanding the whole question of symmetry and the specific condition of situs inversus, a clear differentiation of the types of asymmetry must be kept in mind. Whereas the normal R-handed adult exhibits slight one-sided size dominance confined to the R side of the body and limbs and to the L side of the head, the Schwartz and Greene case, cited above, showed no crossover in the cervical region; the R of the head shared the R sided size increase of the pectoral girdle. One might expect a L-handed person with SIVC to show size-dominance of the L half of the body and R half of the head. However, until more is known of the relation of visceral disposition, skull and face asymmetry, and handedness, it is difficult to predict what to expect in the other possible combinations of handedness with complete and partial transposition of the viscera.

D. Relation of the general problem of asymmetry to SIVC and to practical medicine.

The present paper is concerned only with that part of the general problem of asymmetry which is known as SIVC. There can be little dispute that it represents one phase of the larger study of asymmetry. If any evidence can be brought forward in explanation of the origin of any phase of asymmetry, it should be closely examined to see whether it can supply either an explanation for other phases of the larger study, or a lead toward a mode of study which will supply evidence to provide an explanation. Consequently the evidence given above, indicating that the asymmetry of fowls known as gynandromorphism, is explicable on a strictly genetic basis, is cited as a possible lead in the present study of this special phase of asymmetry.

Medical science concerns itself with the study of disease but principally justifies itself upon the basis that its accumulated knowledge does provide a means of prevention and cure for some diseases. Alleviation of suffering can be attained frequently when the cause of the ailment is not known; but it is not often possible to entirely prevent or cure an afflicted patient when the etiology is disputable. Consequently medical science is continually concerned with the study of causes. One of the most baffling matters in the study of pathogenesis is the cause of the higher incidence of certain pathological conditions on one side in bilateral organs.#

examples: (explanations for some of these have been given; but are not completely satisfactory) - more cerebral emboli to L; two forms of spread in neuroblastoma of

An equally important question is the matter of unilateral localization of bilateral functions within the brain (speech center on the L in R-handed individuals) - a question of great moment to the neurosurgeon.

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adrenal: Pepper type on R, Hutchinson on L; primary varicocele principally on the L; spread gastric carcinoma to supraclavicular lymph nodes of L more than R; aberrant renal vessels are found more often on L than on R; abnormally moveable kidneys are found in 90% of cases on the R; acute pyelitis in women is found much more often on the R than on the L.

II.

DEFINITION

> "Es giebt innere Krankheiten und man begegnet Fällen, die eine chirurgische Operation nöthig machen, wo sich der Arzt und Chirurg Irrthümern aussetzen würden, wenn sie nicht vor Einleitung einer Behandlung der Krankheiten oder einer Operation nach einem gleichen Changement (Transversion) suchten und forschten."

A. General

In complete transposition of the viscera (SIVC), all the organs of the thoracic and abdominal cavities are transposed laterally in mirror-image fashion. Kuchenmeister provides plates illustrating the normal (situs solitus) and the altered (situs inversus) condition as seen in dissection of the viscera. Cleveland's more recent paper has numerous photographs demonstrating the relationships of the transposed viscera.

Synonyms for this condition are many: transposition, transpositio, transpositio viscerum, situs transversus, situs transversus viscerum, inversion, inversio viscerum, situs inversus, situs viscerum inversus, lateral inversion of the viscera, viscerum totalis lateralis rarior solito inversus, inversa corporis structura, anastrophe, bouleversement des visceres, heterotaxia, situs mutatus, situs partium perversus, dislocatio viscerum, dislocatio viscerum lateralis, translocatio, translocatio lateralis viscerum, renversement, and French, German and English variations of the above.

Quoted from Kuchenmeister, page 1: from Sue, 1746. Translation: There are internal diseases and surgical diseases in which the physician and surgeon would make a mistake if they did not seek and discover transposition before initiating therapy or proceeding with operation.

As employed by the present author, HETEROTAXY is a general term signifying any acquired or congenital (and possibly hereditary) dislocation of a viscus. SIVC is therefore one form of heterotaxy, ectopia renalis is another form; gastroptosis is also heterotaxy. The various degrees of partial transposition of the viscera are not considered part of the entity (SIVC) here under discussion and will therefore be ignored except in a section (below) devoted to anatomy.

Situs inversus viscerum completus (SIVC) is the terminology adopted by the present writer.

DEXTROCARDIA is used in the way adopted by Lichtman (158): "cases in which the heart, in its own development, independent of disease and anomaly in surrounding structures, assumes a position in the right side of the thorax with the apex pointing to the right." Dextroposition is the term, then, for DEXTRO displacement dependent on congenital or acquired extrinsic causes. In dextroposition the apex usually does not point toward the R, but rather toward the L, as in normal sinistroposition.

B. Symptoms

Numerous writers have stated that patients with SIVC suffer from diseases in exactly the same proportions as those with normal situs. This matter will be treated briefly in a later section (Pathology). There is almost universal agreement that there are no disturbing symptoms from SIVC. It is inevitable that the curious and intelligent individual with SIVC, living in a world predominantly populated by persons with situs solitus, will seek

an explanation for the unexpected dextroposition of obvious precordial pulsations following exercise.# Nevertheless the patient is unable to diagnose his condition without the aid of a physician - symptoms are not present to indicate the heterotaxy of most other viscera. Here is a translation of Kuchenmeister's remarks on symptomatology:

There is really nothing to say about symptomatology because SIVC is in itself not a pathological condition, and life in general proceeds undisturbed in its normal way.

We can at most say that the individual feels on occasions of excitement, strenuous activity, dancing, etc., the beating of his actively moving heart on the right side.

Furthermore the course of diseases is not altered by the transposition; a scoliosis causes the same complaints in either situs; pneumonia, typhus, etc. remain the same in either; only for the physician will there be unhappiness - if he does not investigate sufficiently to make the diagnosis of SIVC - in order not to fall into clumsy, unnecessary, mistakes and shortcomings in his art.

C. Diagnosis

Here again the careful work of Kuchenmeister may be accepted as a model. He discusses this matter under the following headings:

1 Selbstdiagnose.
2 Die diagnose in alterer Zeit.
3 Diagnose in neuerer Zeit.

One might well add another heading, "Diagnosis since Kuchenmeister". Self-diagnosis depends upon the symptom of right-sided heart beats. Kuchenmeister lists a number of

But Smith and Horton (422) tell of a woman with dextrocardia who attempted suicide at 47 and, unaware of the abnormal location of her heart, aimed "at the place where she thought the heart was situated and where, normally, it would have been situated. The bullet entered.....the fifth interspace, about 3 inches (7.6 cm.) to the left of the sternum.. ...was removed a few days later by a surgeon".

cases from the literature in which this was mentioned. Diagnosis in former times consisted of palpation over the R and L breasts for the apex impulse of the heart and palpation at the rib margins for liver and spleen. Some men tried also to establish the direction of flow in the colon by administering strong purgatives, presuming that a current visibly moving from L to R would indicate transposition of the abdominal viscera.

Diagnosis in recent times, according to Kuchenmeister, included the methods of auscultation and percussion which are incorporated in the present author's scheme outlined below. Since the time of Kuchenmeister special diagnostic methods (x-ray, EKG, etc.) have been added to the physician's armamentarium (cf. below).

1. Clinical Methods

#a. Inspection:

Look for asymmetry of the head, neck, body, and extremities, noting the differences (cf. under Anatomy). The R testicle hangs lower than the L. The apex impulse is transposed to the R side of the chest. The R side of the face and head, the R breast, and the L upper extremity may be larger than the contralateral features. (Direction of hair whorl should be noted.) Scoliosis (concavity) to the L, and posture with the L shoulder lower than the R is to be expected.

b. Measurement:

The reversal of normal size asymmetry will be

But cf. discussion on page 46.

no more obvious when transposed than in the solitus condition, but careful measurement will reveal it. The following measurements are suggested:

1. R and L biceps contracted and relaxed (maximum).

2. R and L arm length (acromion to tip of middle finger).

3. R and L thigh and calf girth relaxed (bilaterally equidistant from a fixed bony point).

4. R and L leg length (trochanter to external maleolus).

5. R and L skull hemicircumference (nasion to occipital protuberance).

6. R and L thorax hemicircumference (midsternal line at level of 2nd rib to spine of the 5th thoracic vertebra).

It cannot be stated dogmatically that R- or L-handedness is independent of visceral position, i.e. that L-handedness does not accompany SIVC. Assuming that all asymmetrical bodily characteristics are transposed in SIVC, it may be stated that most cases (not all cases, because not all individuals with normal situs are R-handed) of SIVC will be L-handed and will show:

1. R biceps smaller than L.

2. R arm length shorter than L.

3. R thigh and calf smaller than L.

4. R leg length longer than L. #

5. R skull hemicircumference larger than L.

6. R thorax hemicircumference smaller than L.

Halperin (cf. under Anatomy) has shown that the L leg is ordinarily longer.

c. Palpation and Percussion:

1) Vessels:

The very careful and expert clinician may find the L carotid, ulnar, radial, and crural vessels (according to Kuchenmeister) larger than the R. The brachial artery and other readily available arteries might be added to this list.

2) Chest:

The heart, examined by routine palpation and percussion, will be found transposed in mirror-image fashion from its usual location to the R half of the thorax. Kuchenmeister insists that the skilled examiner can detect a higher pitch to vocal fremitus over the three-lobed lung (now on the L) than over the two-lobed lung. Cabot and Adams (320, page 211) emphasize "this natural inequality of the two sides of the chest", upholding Kuchenmeister.

3) Abdomen:

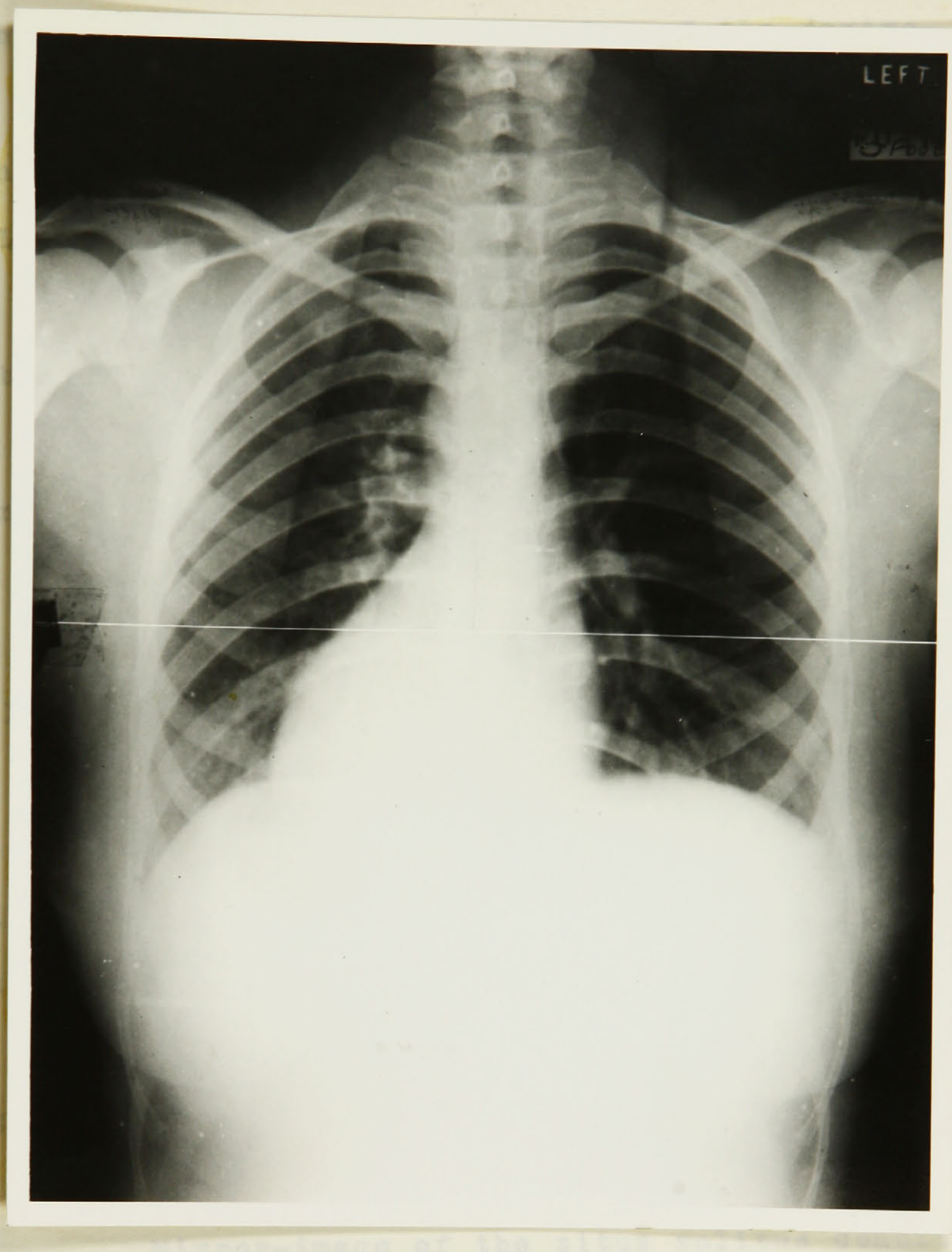
Little can be learned by abdominal palpation unless the subject be asthenic, whereupon the aorta can easily be felt running to the R side of the middle of the vertebral bodies, and the L kidney can sometimes be palpated lower than the R kidney. In pregnancy the uterus will be found more to the L than to the R of the midline.

Percussion is of greater diagnostic aid, revealing the liver on the L, the spleen and stomach on the R.

d. Auscultation:

The esophagus may be found by having the pat-

Illustration I



Chest plate of M.Y. Case II

Dextrocardia of SIVC, showing the apex pointing to the R, in the R mid-clavicular line. The L ventricle is on the R side and the R auricle and R ventricle lie to the L (toward the midline). The aortic knob is on the R. The L diaphragmatic leaf is higher. (Courtesy of Department of Radiology, Royal Victoria Hospital, Montreal).

ient swallow water, whereupon noise from the liquid boli may be localized to the R of the midline. The heart valve areas will be found on the R of the chest in mirror-image of the normal L positions. Confirmation of the dextro-position of the abdominal aorta may be obtained by auscultation.

e. Laryngoscopy:

Kuchenmeister directed that laryngoscopic examination be performed, whereupon the L bronchus will be found to be the larger and the more easily entered, and the carina, to the R of the midtracheal line.

2. Laboratory Methods

a. X-ray:

1) P-A plate of the chest.

Mirror-image of the situs solitus condition will be found, even to the finer details, as revealed by careful anatomical studies. The striking features are the dextrocardia and the higher position of the L diaphragm.

2) Flat plate of the abdomen.

Mirror-image of the situs solitus condition will be found; outstanding features are: sinistro-position of the liver, dextro-position of the spleen, and the higher position of the R kidney.

3) Barium visualization of the G-I tract.

Confirmatory evidence for the mirror-imaging of the normal disposition of the intestinal tract is here provided.

4) G-U visualization.

Confirmatory evidence of the position of kidneys is provided thus, although this is not ordinarily necessary.

#5) Other possible x-ray investigations.

Innumerable possibilities are offered for further investigations of the various body systems, to check on transposition of the normal asymmetry. Thus it is entirely feasible to investigate the cerebral ventricles by pneumoencephalography, the cerebral circulation by angiography, the size of the lachrymal sacs by use of a suitable radio-opaque substance, etc. (Calori, (32) found these structures larger on the R in SIVC.)

6) Electrocardiogram.

The first lead is inverted and the second and third leads are interchanged. A normal electrocardiographic picture can be obtained by interchanging the arm bands.

7) Electroencephalography.

Until work has been done in this field it is possible only to theorize on the results to be expected. (cf. below - Physiology.)

8) Handedness tests. Other lateral dominance tests.

Various objective tests for handedness have been devised. The Phi Test for Lateral Dominance by Jasper and Raney (36) is recommended. Presumably there should be complete reversal of all forms of lateral dominance

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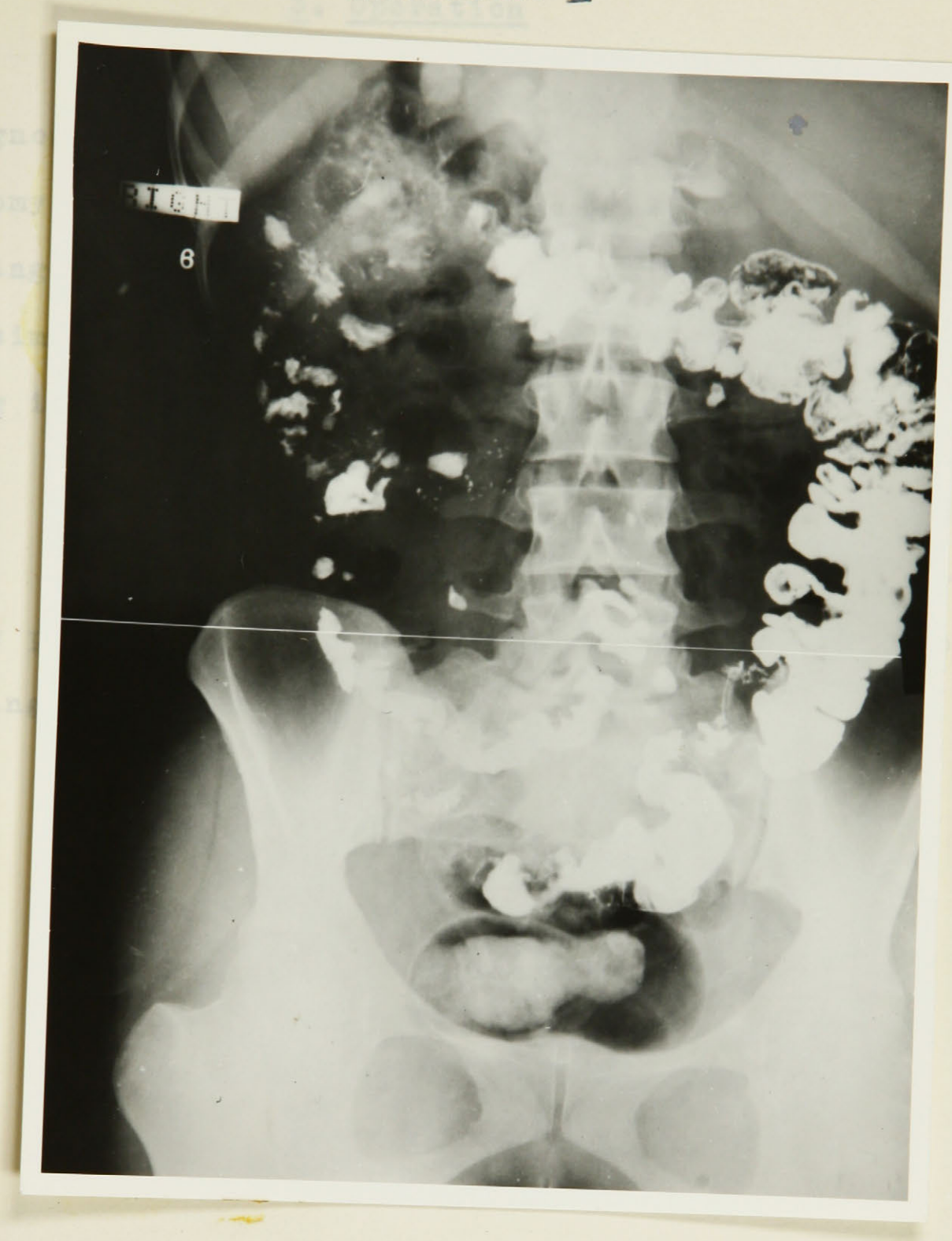
cf. pages 38 and 39.

Illustration II



Barium visualization of the colon of M.Y. Case II

Transposition of the colon is demonstrated. The ascending colon is on the L, rising to the hepatic flexure at the position of the transposed liver. The transverse colon ascends from L to R, ending at the splenic flexure on the R. (Courtesy of Department of Radiology, Royal Victoria Hospital, Montreal).

not determined by training, but dependent upon congenital bodily asymmetry.

3. Operation

There are numerous reports in the literature of diagnoses of SIVC which were first made at operation. Celiotomy is, of course, a very reliable method of determining the position of the viscera. Theoretically it is similarly possible to arrive at the diagnosis by opening into the skull (32-( ) or the thorax.

4. Autopsy

The dissecting room and the pathological laboratory provide opportunities for indisputable evidence regarding visceral disposition.

III.

HISTORY

A. Biblical References.

"Interessant ist, dass Hoffman die Inversion in diesem Falle und in dem von dem oben citerten Mörder mit mord-und Stehlsucht zusammen.....anführt."# (Kuchenmeister). Apparently Hoffman believed that the individuals with a congenitally displaced heart were more liable to commit crime than those with normal cardiac position. The following passages from the Bible were mentioned by Hoffman in support of his argument:

> Psalm 101: "A froward heart shall depart from me: I will not know a wicked person."
>
> Psalm 105: "He turned their heart to hate his people, to deal subtilly with his servants."

B. Early Cases.

Various writers are well satisfied that Aristotle observed SIVC in lower animals. (308) Petrus Servius (303) or Severinus (158) is said to have reported the first case in man, discovered in Rome 1643. But Grieger (118) credits Fabricius with the first case in 1606, and Abrahamson (2) gives the credit to Riolanus. Kuchenmeister gives a very readable history of this subject, undoubtedly based on more extensive research than the statements of most other authors. (It was the author's

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It is interesting that Hoffman related the transposition in this case and in that of the above mentioned murderer, to a passion for murder and robbery.

intention to summarize Kuchenmeister's paragraphs devoted to this, but the book has been recalled by the New York Academy before this translation could be accomplished.)

C. Reviews of the Literature.

Notable articles including comprehensive studies of the literature or extensive reference lists are the following:

Author	Date	Number of cases
Geoffrey St. Hilaire (398)	1832	30
Wenzel Gruber (398)	1865	70
Kuchenmeister (374)	1884	149
Pic (402)	1895	190
Sorge (424)	1906	194
Schelenz (415)	1909	210
Karashima (364)	1912	200
Laubry & Pezzi (377)	1921	227
Cleveland (51)	1926	360
Larson (151)	1938	estimates 435
Bauer (present author)	1942	estimates 700

The bibliography prepared by the present author will not be presented in full for this paper. It includes more than 900 articles, and a conservative estimate of the total number of cases (considering that possibly a quarter of the articles report more than one "new" case; and that only a few articles are published without the excuse of a "new" case) is therefore 700. Not the entire increase from 360 is due to cases published since 1926. Indeed the present author has found many articles not reviewed in previous compilations. Needless to say, not all these articles have been consulted in the original as yet. For this paper a reference list has been provided with:

I. Casuistic bibliography since Cleveland's summary.
II. General references for the text of this paper.

D. Notes on important developments in Etiological Study of SIVC.

The first matter of importance was Senac's division of dextrocardias into congenital and acquired forms in 1749. Not until then had it been recognized properly that several intrathoracic acquired pathological conditions may produce dextroposition of the heart indistinguishable from true dextrocardia without special care in history-taking and examination. The true dextrocardia of SIVC is present at birth; it can be verified by percussion of the transposed liver and stomach and in other ways.

1828 vonBaer ascribed the condition to the position of the embryo on the yolk sac:# solitus if to the L, inversus if to the R.

1832 Serres - viscera interrelated as regards position, in a fashion resembling the interdependence of bodies in the solar system.

1836 Geoffrey St. Hilaire - the liver as the determining organ of the interdependent system causing inversion of all viscera by its mechanical influence.

1861 Forster furthered vonBaer's theory by explaining that double monsters always show SIV on one side--that lying to the R of the yolk sac in embryonic life.

1864 Tacke disproved Forster's claim regarding double monsters, demonstrating that many monsters of this type fail to show SIV in one half.

1865 Dareste proposed the primary cardiac tube as the determining organ for the position of all viscera.

1867 Rindfleisch supported Dareste's idea.

From vonBaer (307): "In dem anderen Falle aber hatte schon der halbe Foetus sich auf die rechte Seite gedreht, die hintere Hälfte war night ganz gerade, sondern eighenthumlich gedreht, als ob sie eine Gewalt erlitten hätte. Das Herz war hier ganz umgekehrt gestellt, die Vorkammer lag nach rechts, die Wolbung der Kämmern nach links, und so war in allen seinen Theilen das umgekehrte Verhältness der Lage, die normale beschreiben werden. Ich kann daher nicht zweifeln, dass hier ein Situs inversus sich zu bilden angefangen habe."

1877 Kolliker joined the position of Dareste and Rindfleisch.

1879 Perls disproved Forster's claim, as Tacke had done.

1884 Warynski and Fol came forward with work on hens' eggs, demonstrating that SIV can sometimes be produced by warming one side of the egg more than the other.

1893 Crampton, and 1894 Kofoid, observing Physa and Planorbis (sinistral snails) were able to determine adult situs from the second cell division on.

1894 Lochte opposed the idea of Dareste, Rindfleisch, and Kolliker by demonstrating cases of partial SIV - destrocardia without associated alteration in any or all other viscera.

1896 Zur Strassen presented evidence from experimental work on ascaris, in the eggs of which he had found about 1 in 35 with inverted situs; in the adults he found 1 in 125. He showed that the situs could be recognized in the 8 cell stage.

1899 Koller denied Forster's statement regarding SIV in one half of <u>all</u> double monsters, but at the same time he adopted his idea of the causation of SIV, stating that it never occurred unless the ovum divided to form two anlagen. Single individuals with SIV were thus explained by the assumption that unequal twinning occurred, the normal twin perishing in utero and forming an unrecognizable mass at birth. There is some question, however, whether Koller should be credited with the elaboration of this idea. In an article by Hadden (352) in 1890 appears a quotation # from Bland Sutton which fully expresses this same idea.

1903 Conklin worked on Crepidula (a dextral snail) and determined the situs of the adult from the position of the first cleavage plane of the ovum.

1906 Speman reported very significant work in experimental embryology, using a transplantation technique on eggs of Bombinator, Rana esculenta, and Triton taeniatus. By removing a piece of medullary plate includ-

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Bland Sutton in Dr. Kingston Fowler's "Dictionery of Practical Medicine":....."and that when twins occur of the same sex, with a common amnion and a single placenta, they are the product of a single ovum. This, of course, suggests that one individual with transposition of the viscera should be one of twins. Unfortunately no facts are forthcoming..... It.....does not follow that because only one child was recognized at birth, therefore only one was present. Many..... the second child was flattened out, and formed merely a small lump in the membrane....."

ing the anlage of the mid-gut (and avoiding the anlagen of head, eyes, heart), replacing it in reversed position, he produced visceral transposition in the developing embryos.

Others who have expressed ideas on the etiology of SIVC since the work of Speman, will be mentioned in the section on Etiology. Dr. Maude Abbott of McGill explained this condition on the basis of the relation of the embryo to its blood supply - an idea essentially the same as that of vonBaer in 1828. The monumental work of Stockard (426) on the relation of developmental rate and teratology formed a basis for more recent theories. Komai, for example, (371) claims that SIV is the result of a disturbance of normal development of the same type as causes small size or "abnormalities".

E. History of SIVC as a Genetic Study.

1. Heritability of SIV

Throughout the entire literature of SIV there has been an attempt to indicate that this condition is a rarity which not seen more than once in a lifetime - certainly not more than once in the same family! Recently this attitude has changed. Gall and Woolf (100) presented a table of cases in which the family history showed more than one person to be affected (cf. Table I, page 25). At the present time additional cases may properly be added to this list (cf. Table II, page 26).

2. Heritability of Asymmetry

Sumner and Huestis (427) were the first to record definite ideas on the possible physiological-genetical basis for asymmetrical characters. "We may suppose the

TABLE I

	AUTHOR	YEAR	SEX	AGE	RELATION	PROOF	REMARKS
1	Rogi	1880	f	20	sibs	hearsay	
			m	34		P. X.	
2	Carpenter	1904	m	?	sibs	?	"cited by Lichtman"
			m	?		?	
			m	?		?	
3	Doolittle	1907	m	41	father	P.X.	sister has twins with dextrocardia?
			m	?	son	hearsay	
4	Reid	1909	m	?	sibs	hearsay	
			m	?			
5	Lowenthal	1909	m	?	sibs	hearsay	
			m	?			
6	Leroux, Labbe and Barret	1912	m	7½	sibs	X-Ray	
			m	13		X-Ray	
7	Reinhardt	1912	m	20	twins	X-Ray	
			m	20		X-Ray	
8	Neuhof	1913	f	?	sibs	autopsy	died of tuberculosis
			m	26		X-Ray; EKG	
9	Curschmann	1919	m	22	sibs	X-Ray	
			f	17		X-Ray	
10	Ochsenius	1920	m	6¾	sibs	X-Ray	
			f	13		X-Ray	
11	Brimblecombe	1920	f	12	sibs	X-Ray	
			m	10		X-Ray	
12	Frohlich	1922	f	4	sibs	operation	celiotomy for appendicitis
			m	2		X-Ray	
			m	1		X-Ray	
13	Hofmann	1926	f	19	sibs	operation	peptic ulcer expected; G.B. found
			m	12		X-Ray	
14	Liotta	1927	m	17	sibs	X-Ray	C. H. D.
			m	?		X-Ray	
			m	?		X-Ray	
15	Bianchi	1927	m	21	sibs	autopsy	
			f	30		P.X.	
16	Gall and Woolf	1934	f	2	sibs	X-Ray; EKG	
			f	4 mos.		autopsy	

TABLE II

	AUTHOR	YEAR	SEX	AGE	RELATION	PROOF	REMARKS
17	Meyer and Hurlimann	1916	m m		father son	P.X. and hearsay	
18	Gunther	1923-4	ff		sibs		
19	Cahan	1925	m f	28 23	sibs	P.X.; X-Ray and EKG	
20	Oshima	1929	mmm		sibs		
21	Muller-Pollak	1929	ff		sibs		
22	Mittlebach	1930	ff		sibs	operation	
23	Matisson	1933	f f		mother daughter	P.X.; X-Ray P.X.; X-Ray	
24	Feldman, W.M.	1935	m f f	7 13 24	sibs	X-Ray X-Ray; operation X-Ray	
25	Manson	1935	mf		sibs		
26	Korner	1937	mm		sibs		
27	Pernkopf	1937	m ?		father offspring	N.R. autopsy	(partial SIV?)
28	Cockayne	1938	mf		sibs		
29	idem	1938	mf		sibs		
30	Feldman and Needle	1940	f f	10 12	sibs	P.X.; X-Ray P. X.; X-Ray	

From the above list of 30 cases, three must be excluded. Carpenter's case is not SIVC, but acquired dextroposition of the heart (although it is misquoted by Lichtman and by Gall and Woolf); there is no family history of SIVC in the original. Reinhardt's case is excluded because it will be included elsewhere in a separate listing of cases in twins. The cases of Muller-Pollak and Mittlebach, on investigation, prove to be the same family, consequently one must be excluded in a listing of families.

existence of eggs in which the materials responsible for more rapid growth passed indifferently to the right or the left side of the body, at (or before) the time of the first cleavage. This would result in an inherited asymmetry, indifferent as to whether dextral or sinistral. Finally, the cytoplasmic substances with which the paternal "gene" combined might be disposed without any relation to the main axis of symmetry." These authors believed handedness may have no relation to situs inversus, "and while the latter condition may not be inherited (of this we have no certain knowledge) the normal position of the viscera certainly is hereditary, in the same sense that any other major feature of our organization is hereditary".

In support of the idea that asymmetry (of various features) is heritable, Sumner and Huestis cite several examples in man:

1. Weisman, A. - pinhead-size depression anterior to L ear, 3 generations.
2. Schofield, R. - R ear bilobed, 4 generations
3. Authors' - divergent squint L eye in proband and numerous relatives
4. Jordan, H. E. - large collection of families with L-handedness.

Additional support is to be found in the reports of heritable asymmetry (cf. Introduction: Asymmetry in Biology) in other animals. Of such reports the discussion by Goldschmidt (347) provides a good summary (pages 221-7)

Lichtman (158) writing on isolated dextrocardia in man drew upon case reports of SIVC and dextrocardia to provide a proper survey of the possible etiological factors. His article, written in 1931, at least serves to establish

the approximate date of the end of the period during which SIVC was considered a definitely non-hereditary character; for although he did not attempt to prove or disprove the case, he seriously considered this question.

In 1933 Matisson (179) reported a study of a family with situs inversus in 2 members for each of 2 generations. He examined 488 persons, finding the frequency of L-handedness not sufficient to be considered characteristic of families with SIVC. So far as is known this is the only study of such an ambitious scope.

The collection of families made by Gall and Woolf in 1934 has been cited. The original paper for several of the cases is not available at McGill. However, insofar as facilities permit the material has been checked; only the case of Carpenter (as explained above) should be discarded. That leaves 28 case histories (of varying reliability) of families with more than one affected member (leaving out Reinhardt's case in twins - to be treated separately below.)

In 1935 W. M. Feldman submitted to the editor of the Proceedings of the Royal Society of Medicine, England, a case report of SIVC (88). It may be that Cockayne, then senior editor, influenced Feldman in his study of this family, in which he examined 5 out of 12 children and their parents - finding the latter normal, and 2 of the proband's sibs affected. At any rate Feldman acknowledges the advice of Cockayne that, on the basis of his pedigree, SIVC is probably a recessive trait.

Cockayne's article of 1938 (52) is the next item of particular interest. It is notable for being the first report dealing strictly with "The genetics of trans-

position of the viscera". Its author sets up certain criteria for recessive traits, then proceeds to test his evidence drawn from reports in the literature and reinforced by a large personal, unpublished series of cases, by these standards. He concludes that "Complete transposition of the viscera is inherited as a recessive and is determined by a single autosomal gene. Proofs of this are its familial incidence and general distribution within a family, its occurrence in both members of a pair of monozygotic twins, and the high percentage of first-cousin marriages that give rise to it (six in 52 consecutive fraternities). The ratio of affected to normal sibs in the fraternities, so far as this can be ascertained, agrees with that expected of a recessive character."

Cockayne's paper does not therefore present the final word in this matter; he has written: "....the ratio of affected to normal sibs so far as this can be ascertained." For his analysis, he has collected 119 available fraternities. He counts as normal all members not examined! - "omitting those who died in early infancy, as shown in the second table, the ratio is 1:2.9, and, including those who died in infancy, it is 1:3.1". He feels that the material from the literature is not a random sample, and uses for further consideration his own series of 53 fraternities "collected by the courtesy of many medical men in this country and overseas....." It is unfortunate that Cockayne could not have access to more material, so that he might personally investigate 53 or more fraternities. Where many different men, untrained in this work, gather

data even on the basis of written instructions (reaching them by mail) the resulting material is less reliable than where one well-trained individual can personally supervise, or individually examine. There is evidence, furthermore, from Cockayne's 1940 paper, to show that physical examination is relied upon for the establishment of the diagnosis of situs in supposedly non-affected members of the family (and not x-ray examination): ".....Dr. James Graham kindly examined the parents and the surviving brothers and sisters and found that in all of them the heart was in the normal position# and no cardiac abnormality was present". Indeed an experienced physician should, upon examination alone, be able to diagnose SIVC, more particularly if he is examining the patient with that diagnosis in mind. Nevertheless, for work of this nature, especially when fraternities cannot be seen personally, it would not seem out of place to obtain from collaborators an objective record (x-ray) of the situs of each member of each fraternity.

In summary, then, Cockayne's paper has given a very good indication of the probable mode of inheritance of SIVC, but the final conclusion will probably await the analysis of data of a series of cases more reliable because individually studies by more objective methods.

Goldschmidt (347) includes a consideration of asymmetry in his textbook, citing examples of genetically determined asymmetry, some of which appear to have direct

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cf. criticism on page 44.

relationship to the problem of the physiological genetics of SIVC. Of Lymnaeus (sinistral snail) he writes: "in these lines, right-handed forms also occur which are not hereditary. Whether this is caused by modifiers or by different alleles for left-handedness, in some way an embryonic (here cellular) situation near a threshold line must be involved, which might be transmitted or not by some individuals according to genetic conditions controlling a process involved in the threshold." Under "Constant asymmetry of an alternative type" (such is SIVC), Goldschmidt cites (page 224) "a nonheritable variation to the other type.....the frequency of which might be hereditary." For the heritable cases of this type he assumes "The presence of a strictly alternative situation at some point of embryonic determination where a determining material for the formation of an organ or for controlling a threshold may go only to the left or to the right".

Rashevsky (406), in 1939, in "Some remarks on the mathematical biophysics of organic asymmetry" considered the "problem of asymmetric organic structures in general" and "the preponderance of one type of asymmetry". His considerations are important in any contemplation of the possible physiological genetics of SIVC. Two possible physical factors in embryonic development are considered in this paper: "one, considered biophysically rather unlikely, is based on the asymmetry of the electromagnetic field; the other, considered more plausible, is based on the asymmetric structure of organic molecules and on the resulting asymmetry in the diffusion fields of those

molecules".

Cockayne was troubled in 1938 by the presence in the literature of a case by Dubreuil-Chambardel (76) reporting SIVC in one of a pair of monozygotic twins. "If a condition is inherited either as a dominant or a recessive, it should affect both members of a pair of monozygotic twins, or neither." (52) Further: "There appears to be only one record of its ((SIVC)) occurrence in one member and not in the other." He finds it difficult to explain this case, in view of his other conclusions. "There are at least two possible explanations, loss of the whole or part of an autosome (one member of a pair of corresponding chromosomes), or somatic mutation .....On the first hypothesis, at the first cleavage of the zygote the whole chromosome, or that part of it which carried the dominant gene for normal rotation, was lost to the cell from which the tissues of the twin with transposed viscera were derived, but not to the cell from which the tissues of the normal twin were derived. On the second hypothesis, just after the first cleavage the dominant gene for normal rotation mutated in the cell from which one twin arose, making it homozygous for sinistral rotation, but no mutation occurred in the other. The mutation would be the same as that by which transposition has arisen from time to time, but instead of taking place in a germ cell it took place in a somatic cell."

By 1940, however, Cockayne had been able to contact girl twins who presented the picture Dubreuil-Chambardel had reported. Furthermore, he found three additional sim-

ilar reports in the literature, purporting to be monozygotic twins. Thereupon he wrote: "Transposition of the viscera in man is recessiveto the normal arrangement, and elsewhere I have suggested (1938) two ways in which it could affect only one member of a pair of monozygotic twins. Apart from the improbability of so unusual an occurrence happening in at least five recorded cases, neither explanation accounts for the occurrence of other minor mirror image arrangements, and any genetic explanation must be abandoned." (53) This paper will be discussed in detail below.

3. Family History Data in reported cases.

Following the literature chronologically, the reader will discover that although the interest of medical men in heredity lags behind the advances being made in medical genetics, nevertheless the influence of such advances is apparent in the information to be found in recorded cases of SIVC. As an example: in the first seventy (approximately half) of Kuchenmeister's cases, covering the literature from 1643 to 1835, mention of the family history appeared in only five:

1. Bore 16 children.
2. 8th child of a very nervous mother
3. His brother's heart beat in the left side as normal.
4. Two other relatives at post mortem showed normal situs.
5. Married and childless.

In a random sample of cases reported during the last cen-

tury, there was a complete lack of information about the family (not in 65 out of 60, as above, but) in only 35 out of 60 - slightly over one half. More recent cases (since the beginning of genetics as a science) show the influence of the new science by the inclusion of specific items of information such as the age of parents, number of sibs, health of parents and sibs, etc.

As the reviewer surveys the present store of information in the libraries of medical science, however, one important fact is presented: more than half of the recorded cases are completely valueless for genetic study (i.e. include no family history data). Careful scrutiny requires the elimination of a majority of the remaining cases because the items of information do not include sufficient data about the immediate family. (A thoroughly scientific study must reject all but a handful of the remaining ones[#] because, except in that handful, the knowledge of the relatives of the proband is based on inacceptable evidence).

F. Montreal cases of SIVC

The present paper is not the first evidence of interest in SIVC by men in Montreal. Dr. Abbott's idea regarding the etiology of this condition was referred to above (page 24). But earlier still, an assistant demonstrator of clinical medicine at McGill, Dr. T.P. Shaw, reported the case of a man of 23, diagnosed by physical examination (no family history given). This was in 1895

cf. pages 44 and 45.

Fry in 1903 reported a 15 year old girl from Dr. C.F. Martin's outdoor clinic. (391) Fry stated that the family history was "irrelevant". His diagnosis also rested on clinical examination alone. A famous McGill physician and poet, Dr. John McCrae, reported three cases, all from the Teaching Hospitals at McGill. In two of these there is no family history. The third concerns a 49 day old male from the Foundling Hospital. He was the 15th child of a 46 year old mother (mentally dull) who had hare-lip and a systolic murmur widely audible over her chest; there were no abnormalities in the other children (not examined) according to the anamnestic data. This case is notable for the curious finding that the visceral transposition was complete in all particulars <u>except</u> the gall bladder! All McCrae's reports include evidence from post mortem examination. (385, 386).

The other recorded cases of SIV from Montreal (313) both came under Dr. Maude Abbott's observation. Beattie, then assistant to Dr. Abbott as curator of the McGill pathological Museum, reported one in 1922, being chiefly interested in the congenital cardiac anomaly. He states that the child was "a case of a blue baby with situs inversus viscerum", but Dr. Abbott later on (302, page 239) listed this case under "dextrocardia with <u>partial</u> situs inversus". No detailed description of non-circulatory viscera is given, no family history.

Abbott and Moffatt ( ) reported the 7th Montreal case in 1929. It concerned a 14 year old girl who died of congenital heart disease at the Royal Victoria

Hospital. She was a first-born child, daughter of a father suffering from a "bad heart" and a "well" mother. Autopsy evidence supplements the clinical diagnosis which was based upon physical examination, x-ray, and EKG. Dr. Abbott regarded this also as partial transposition of the viscera, not SIVC.

The series of cases under study by the present author, numbers nine from Montreal. Not all of these are available immediately, but so far as can be determined at present they are persons who have not been studied before and they are unrelated to the recorded cases from Montreal. Among the cases seen in Montreal and elsewhere, the present author has studied ten, altogether, and found among these ten not a single case of partial situs inversus. This observation provides a rough idea of the relative incidence of partial and the complete situs inversus. This idea must, however, be influenced by examining the total list of cases reported from Montreal as reviewed above. With the present author's series of nine cases based on x-ray evidence, there is a total of sixteen cases to review, two of which are partial situs inversus. These two cases of partial situs inversus were subjected to post-mortem examination, as recorded by Beattie and Abbott and Moffatt. McCrae's three cases were subject to postmortem examination. The two cases of Shaw and Fry, listed as complete situs inversus, were based on physical examination. Consequently, there seems to be no reason to doubt the authenticity of the report in fourteen of the sixteen cases. The instance of partial situs inversus thus being two out of fourteen.

IV

PRESENT KNOWLEDGE

A. Frequency.

No accurate idea of the frequency of SIVC has been derived from the incomplete knowledge provided in the literature. Note how inconsistent are the figures quoted by various authors:

Gruenfelt (350) 1889	1:10,000	army recruits
McCrae (385) 1906	1:2,000	autopsy
Sherk (421) 1922	1:34,700	Mayo clinic admissions
Lewald (156) 1925	1:35,000	recruits (physicals)
idem	1:5,000	x-ray
Cleveland (51) 1926	1:10,000	anatomical dissection
Mandelstamm and Reinberg (171) 1928	1:1,230	
Rosler ( ) 1930	1:7,467	

B. Reasons for reporting cases of SIVC.

1. Rarity

Any nosological entity which is represented in the known medical literature by more than 500 casuistic articles (cf. this article, page 21), should no longer be regarded as a rarity.

2. Anatomical study

The early literature concerned itself with careful anatomical descriptive details of cases discovered in the morgue or the anatomical laboratory. The meticulousness of especially the German observers is recorded in Kuchenmeister's monograph. Aside from details of the distribution of certain nerve plexuses# there appears to be

cf. under Physiology, page 56.

nothing essential yet to be recorded. Such work as that of Arnell (306) in 1935 may contribute further knowledge of great theoretical importance. Arnell stained sections of the spinal cord from Thoracic I to Sacral V and made fiber counts bilaterally, showing that the number of fibers was greater on the R than the L in a R-handed man of normal situs. Similar counts carried out on a large series of cases are needed before any conclusions are permissible; and it would be interesting to determine by such fiber counts whether handedness and visceral situs are anatomically related or independent.

3. Physiological study

Apparently very little is known of the physiology of asymmetry. Here indeed is a large gap in our knowledge of SIVC. Brief mention of some available facts is given below. There is good justification for the publication of further studies of SIVC which include observations on asymmetrical physiological functions in paired organs. It is reasonable to expect that women with SIVC will deliver their children ROA more than LOA, just as the woman with situs solitus delivers more by the LOA mechanism than by ROA. It seemed reasonable to early observers to expect L-handedness; this question has not been answered finally, and further reports could contribute a great deal.

4. Pathological study

Contributions to the literature which include observations regarding the Kartagener syndrome of bronchiectasis, sinusitis and SIVC or other syndromes or patho-

logical conditions which may prove to be peculiar to the transposed condition of the viscera, will be well worthy of places in the medical journals. The etiology of bronchiectasis is discussed in a recent paper by Diamond and Van Loon (332). In 63% of the cases a specific antecedent illness (pneumonia, pertussis, measles head the list) is given; congenital weakness of the bronchial muscle is mentioned fifth in the list of causes. However, their statement that the failure of dilations to develop in 75 patients who had the same infectious etiologic factors and who developed only tracheobronchitis, suggests a congenital basis in the children with full blown bronchietasis. This tends to support the idea that the Kartagener syndrome may be an entity with a true developmental basis. Whether this is really so could be determined by an experimental approach: all cases of SIVC to be x-rayed after the introduction of lipiodol for the visualization of the bronchial trees. Note that in Case I the proband has twice had "pneumonia" while his normal brother has not had pneumonia. It would be enlightening to learn from x-ray studies whether any bronchial dilation exists in the proband - if it does, the past diagnosis of "pneumonia" (at least the second time) may be open to question. Both boys had measles at 6 and pertussis at 8. Case III offers a further possibility for the disclosure of important information inasmuch as this child is in its first year of life and has not yet suffered from measles, pertussis or pneumonia. If dilations were revealed in this child (and in a reasonable number of other such children) it would be an indication in support of the congenital

nature of the bronchiectasis in the Kartagener syndrome.

The other matters dealt with in this paper under Pathology all require further study: congenital heart disease, cryptorchidism, associated malformations...etc.

5. Etiological study

This is the most unsettled problem of all. The history of this branch of the subject has already been outlined above. The reader can readily formulate an idea of the difficulties encountered by the reviewer, in attempting to arrive at a sound theory. Actually the work so far recorded is not sufficiently extensive and intensive. The future must provide thoroughly objective studies which will supply not only complete family histories, but also control data covering other possible etiologic factors so that (cf. Goldschmidt [47], page 224, as quoted on page 30 of this paper) the possibility of drawing false conclusions from non-hereditary variation occurring with a frequency which might be interpreted as hereditary, may be obviated.

The question is complicated, of course, by many issues which may sometimes be regarded as side issues, but which (handedness, mirror-imaging, SIVC in one only of monozygotic twins) indeed may provide a clue to the central issue. Consequently any well studied cases stressing this aspect of the subject should be reported.

Contributions will continue to be made by biological material other than man. However "it is doubtful how far it is wise to draw deductions from observations

and experiments on the hen's egg" as Ballantyne (308) page 604) remarked in 1905, in commenting on the 5 day chick embryo with inverted viscera recorded by E. d'Alton cited in support of vonBaer's theory. Nevertheless the ubiquitousness of asymmetry in biology bespeaks a generality of cause or causes and therefore such contributions must be heeded and carefully appraised.

6. Surgical study

"While transposition of the viscera may have no prejudicial effect upon the life and health of the individual, it may prove an awkward complication in surgical procedures. It is easy, for instance, to understand how the success of a colotomy (for intestinal obstruction) might be imperilled by its non-recognition by the operator. In the performance of an oesophagotomy, of paracentesis thoracis, and of operations on the liver, gall-bladder, stomach, pylorus, and spleen, the presence of situs inversus would necessitate changes in the mode of procedure." (Ballantyne, page 601).

Ballantyne's statement is upheld by the recorded cases of appendectomies and cholecystectomies performed through improperly placed incisions or through proper incisions made after a contralateral wound had been sutured. Explanations for the mistake vary widely, but the favorite theme is that SIVC does not include inversion or transposition of the nervous system. Without here reviewing either the series of pertinent cases or the important literature on visceral pain which must be studied in conjunction with these, it may be stated that this question is

of great theoretical importance for general and for neurological surgery and that conclusive work has not been done on this aspect of SIVC.

7. Editorial policy

Intermittently the cry against the multiplicity and the expansiveness of medical journals arises. There must be some wise manner in which that healthy cry can be answered. In the above 6 subdivisions of this section an attempt has been made to indicate, based on a review of a large portion of the 900 articles on SIVC now in the literature, what information is still needed. Mere case reports are undesirable when a subject is already so thoroughly reported. There may be very little more to be learned regarding the anatomy of SIVC. It would perhaps be wise for editors to refuse articles on SIVC that do not constitute genuine contributions to the literature because they fail to include data now recognizable as essential to an understanding of the physiology, pathology, etiology, and surgical, pathological physiology of SIVC.

In a later section will be presented as the general outline, the method employed by the present author for use in appraising (and gathering data from) reports of others in the extant literature. Modifications and elaboration of that outline would be necessary depending on the particular phase of the subject under intensive study, but it contains headings for information especially valuable for the advancement of knowledge of SIVC.

C. Evidence constituting proof of SIVC.

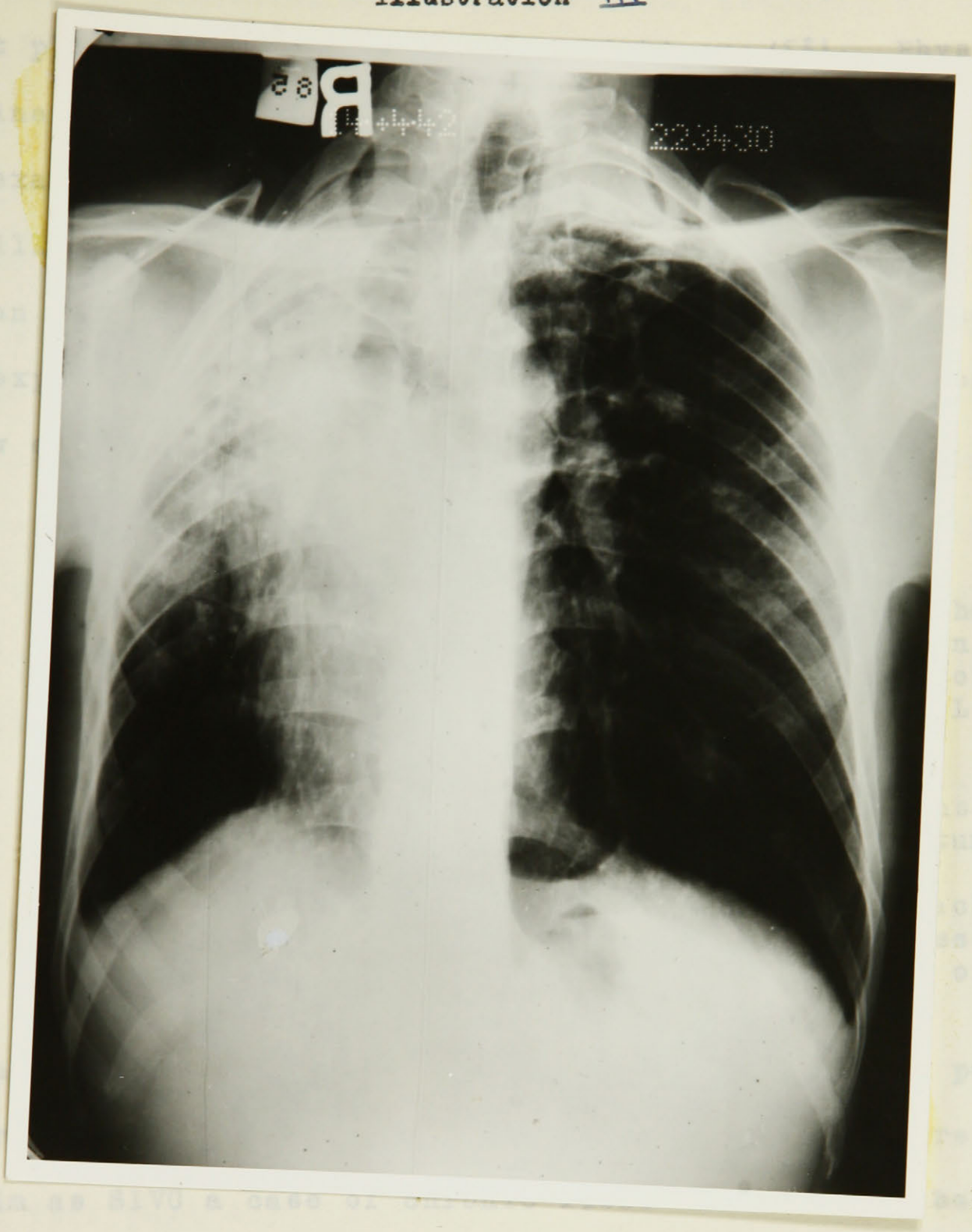
Inasmuch as SIVC is defined in anatomical terms, there can be no gainsaying proof offered either by anatomical or necropsy dissection. Latterly however, most cases have been reported in persons still living. Many of these have been investigated surgically. When the operation (as is the usual situation in the reported cases) involves the abdominal cavity, the well-oriented surgeon can usually determine whether his subject has transposition of the abdominal viscera; but such transposition by itself does not constitute SIVC. Information from celiotomy must be supplemented by evidence regarding the situs of thoracic viscera. Where x-ray investigation of the chest routinely precedes surgical intervention, as (except for emergencies) in many large hospitals today, and where care in marking films "R" and "L" is taken, reliable evidence about the thoracic viscera is readily available. As previously outlined (page 13) there are other procedures to substantiate x-ray proof which in itself is not pathognomonic.

Foggie (337) gives criteria for the acceptability of the diagnosis of genuine dextrocardia in cases reported on clinical grounds alone (no autopsy, no EKG, no laryngoscopy, no lipiodol study...):

1. Dextroposition of the heart beat (etc.) must be present at birth. If not noted at birth, the personal history must be free of thoracic diseases which might cause displacement, and the physical examinations must support such a history (free movements of the heart and lungs, equal respiratory murmur on the two sides, and no change in shape or size of the chest to suggest past disease).

2. X-ray examination of the chest showing the heart axis to the R and a free diaphragm.

Illustration III



Chest plate of J.P.

Infiltration extending from R apex to the fourth R interspace; trachea retracted, along with the heart and mediastinum, to the R. Diagnosis: chronic bilateral tuberculosis, more marked on the R, far advanced. (Courtesy of Department of Radiology, Royal Victoria Hospital, Montreal).

For SIVC one might add the requirement of radiological evidence of abdominal transposition as provided by a barium series (level of the diaphragmatic leaves noted in the chest plate is <u>insufficient</u> - cf. Lichtman: 158). Physical examination can be shown to be extremely untrustworthy. For example, the Pontiac case reported by Munson (cited by Arneill:303) in which the sinistroposed liver was mistaken for an enlarged spleen and the dextroposed heart was noted and explained as being due to dilatation. Gruber records a few errors in diagnosis (all cases of SIVC). (348)

1. Pain in the R hypochondrium explained as chronic hepatitis.

2. A duel wound in a soldier was found in the R hypochondrium; because he vomited green fluid this was diagnosed as penetration of the liver (which, of course, was in the L hypochondrium instead).

3. A Wurzburg Clinic case in which the transposed liver was diagnosed as a splenic tumor.

4. A hard tumor of the pylorus of the stomach, felt in the L hypochondrium, and diagnosed as a cancer of the pancreas or the body of the stomach.

Pedone (216) in 1928 reported a case misdiagnosed as pulmonary tuberculosis. The present author had referred to him as SIVC a case of chronic fibro-ulcerative tuberculosis with acquired dextroposition of the heart (cf. Illustration III).

In view of the frequency of missed diagnoses in cases of SIVC, there should be no objection to insistence upon truly objective criteria for the establishment of the diagnosis in new and in recorded cases, before they be considered as acceptable for inclusion in any scientific investigation on this subject. (The late Dr. Maude Abbott

excluded from her celebrated studies of CHD all cases in which autopsy proof was lacking). The establishment of criteria as indicated above (dissection, autopsy, or combined x-ray and anamnestic data) necessitates the elimination of much of the existing casuistic literature. It excludes most of the family history studies reported up to the present, for how can one accept physical examination alone as a basis for the diagnosis of situs solitus in the family if such examination alone is not acceptable for the diagnosis of SIVC? Intercurrent thoracic disease can as readily cause sinistroposition of a congenitally dextroposed heart, and consequent false diagnosis as situs solitus, as it can cause dextroposition of a congenitally sinistroposed heart.

The cases reported by the present author represent studies supported by evidence which meets the criteria herein proposed, both for the proband and for his relatives, as indicated below.

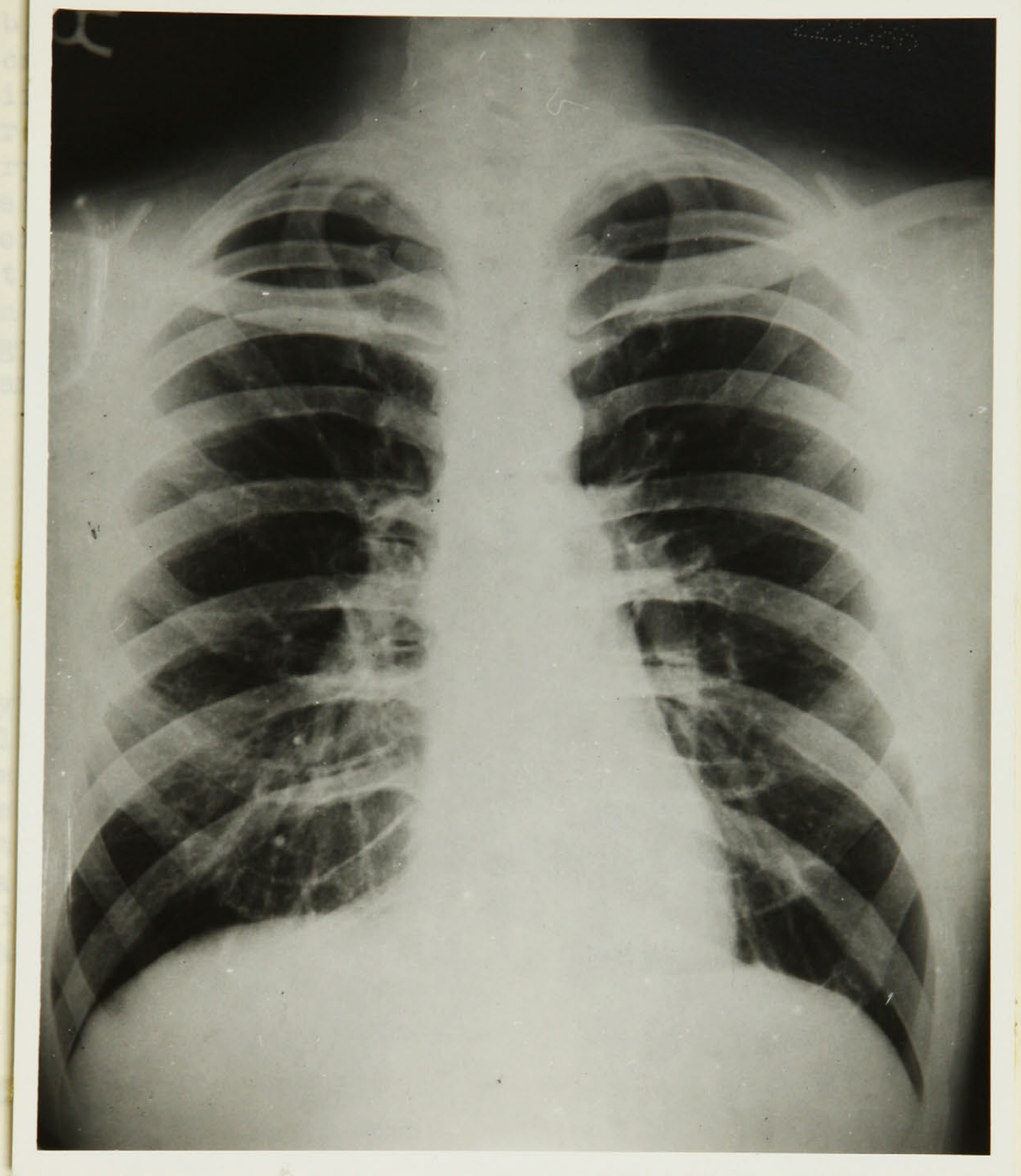
D. Outline form for case studies of SIVC.

The use of this form has already been explained above (cf. page 42)

OUTLINE FORM

(Author)
(Reference)
Age Sex Race
Complaint
Personal History
birth and infancy
postnatal disease (especially pneumonia, pertussis, measles, and intrathoracic pathological conditions; sinusitis)

Illustration IV



Chest plate of V.H.

Normal sinistrocardia in the twin brother of Case . The apex points to the L in the L mid-clavicular line. The aortic knob is on the L. The right diaphragmatic leaf is higher. (Courtesy of Department of Radiology, Royal Victoria Hospital, Montreal).

Evidence for Diagnosis of SIVC
- dissection
- autopsy (cause of death?)
- clinical
- laboratory

Surgical Procedures and Findings
- clinical localization of pain
- objective tests

Complications
- sinusitis
- bronchiectasis
- cryptorchidism
- hernia
- congenital heart disease
- etc.

Handedness, eyedness, etc. (lateral dominance)

Etiology
- Family History (by objective means, at least as regards sibs and parents)
  - birth order (conception rank)
  - age of parents
  - size of family
  - miscarriages and stillbirths
  - multiple births
  - malformations
- Syphilis
- Alcoholism
- Maternal disease in pregnancy
- Geographical environment

Complete data from all hospital admissions
- maternity admissions of proband - course of labor
- visceral pain in non-surgical admissions
- chronic complaints, especially of undiagnosed conditions.

E. Anatomy

1. Introduction

In devoting several pages to the anatomy, physiology, and the pathology of SIVC, it is the author's purpose:

a. to amplify the definition given earlier

b. to provide a basis for a differential diagnosis

c. to lay a background for the consideration of the etiology

A consideration of the genetics of SIVC must be preceded by an evaluation of methods for rigorous identification of the nosological entity under study. Although SIVC

(in its uncomplicated form) is not a disease, and although - as will be shown hereafter - it may be only an end point in a series of alterations from the normal situs solitus? condition, it may nevertheless be treated as an entity. Other investigators have established the precedent of considering SIVC separately from partial transposition, the various degrees of which are (by them) lumped together as an entity. The discussion of the genetics of transposition will, in the present paper, concern only the extreme variants (SIVC and situs solitus) of a possible continuous series.

2. Elaboration of the definition

A detailed description of the asymmetry of the normal situs would serve as well to describe the anatomical features which are of importance in defining SIVC. Chudnoff and Shapiro (96) recommend the studies on situs solitus by Barclay (310) and by Todd (430). As in any other medical study, the abnormal is not well appreciated until the normal is perceived and understood. Kuchenmeister realizes this fully in his 96 pages devoted to an elaborate discussion of the contrasting anatomical details of the normal and transposed condition.

neck	10 pages
thorax	40 "
diaphragm	2 "
abdomen	42 "
genitalia	2 "

There is nothing in Kuchenmeister about the head, extremities, or breasts. It may be objected that according to the terminology adopted by the present author

Illustration V

Split photograph of R-handed person with situs inversus. Case I

The double L face is on the L. This is obviously smaller than the double R face. The normal R-handed person is expected to have skull and face size asymmetry favoring the L side. L.H., however(cf. text), is known to have begun life as a L-handed person.

alteration in the anatomical details of these structures which are not ordinarily considered as viscera need not be considered. However that may be, it is a fact that "even in the cranium there are signs of inversion" (Ballantyne, page 597)

a. Head

In discussing diagnosis, Kuchenmeister recommends mensuration of the skull as an indication of the dimensions of the enclosed brain; indeed he advises sending the patient to a hatter for accurate delineation of the skull shape. He cites a case of a right-handed person with SIVC whose skull measurements demonstrated that the L side was larger than the R.

Liebrich (379) has shown that facial asymmetry is a constant and characteristic feature, more pronounced in peoples in the higher scales of civilization. "It is now common knowledge that the left half of the skull and the left side of the face are larger than .....the right. The left frontal bone is better developed.....etc.", according to Halperin (353).

Calori found the R half of the head larger in SIVC (cf. page 18). Galinsky (342) found the L half larger - his, like Kuchenmeister's case, was a R-handed person, and he concluded that the head asymmetry depended on handedness and was independent of visceral situs.

Conclusions in this regard must await further experimental observations. The author has adopted a method, from the work of others on twins, to demonstrate at a glance, the facial asymmetry. Illustrations are provided herein. L.H., the proband in Case I, demonstrates this

asymmetry clearly and shows that his skull is larger on the R than on the L. This at once suggests that he is L-handed, whereas in reality he is R-handed. L.H. states that he was forced to change his R-hand in the 4th grade, that he can still play hockey R- or L-handed, but that for writing, work, and other play he is completely R-handed. Here then, is a situation not covered by Galinsky's conclusion unless that be amplified or modified.

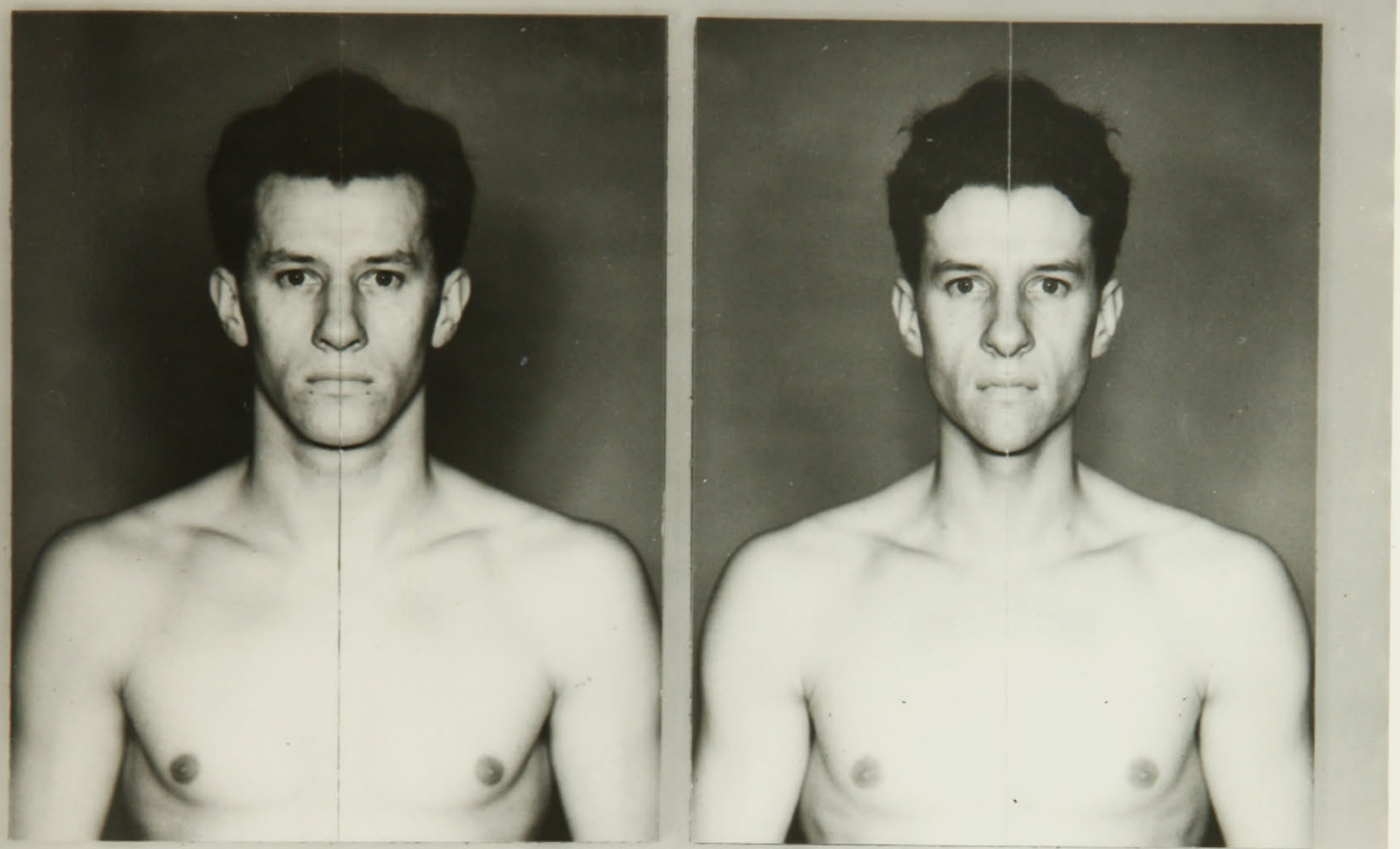
The illustrations are made by accurately splitting from top to bottom in the midline#, a full face photograph and thereafter combining each half with similarly produced halves of a second print made by reversing the negative. The resulting pictures are two entirely symmetrical, unlike faces: one which is bilaterally R and the other bilaterally L. The same technique is being used in further studies of the trunk and neck asymmetry. The great importance of the neck region in differentiating types of asymmetry has already been mentioned (page 8).

b. Extremities

Halperin (353) states that "measurements of the upper extremities demonstrate that the bones of the right side are somewhat longer and slightly thicker than those of the left. The length of the right upper extremity may exceed that of the left by 1 cm., or even by 2 cm." The opposite is true of the legs, the left being more often the longer.

Naturally great care must be used in the choice of anatomical markings to designate the midline in an admittedly asymmetrical object (the face). For the present the philtrum and nasion are being employed in the belief that these points are little affected by trauma and other causes of acquired asymmetry.

Illustration VI



Split photograph of R-handed person with situs solitus.

The double R face is on the R. It is clearly evident that this is smaller than the double L face. What is not so clear, however, is the apparent increased size of the L pectoral girdle and chest over the R. Measurements (cf. text) demonstrate that the R is really larger than the L.

Kuchenmeister advocated measurements of the arms and legs and gave the following as examples of actual cases:

1. Situs solitus, R handed:

L arm	14	cm.	R arm	15	cm.
L calf	21	cm.	R calf	22.5	cm.

2. SIVC, R handed:

L biceps	22.5	cm.	R biceps	24.5	cm.
contracted	25.0	cm.	contracted	26.0	cm.
L calf	31.5	cm.	R calf	32.5	cm.
L arm length	69.75	cm.	R arm length	70.75	

In case I of the present series the following results were obtained (L.H. being apparently a naturally L-handed individual whose training has made him R-handed): #

L biceps	155	~~cm.~~	R biceps	159
contracted	173	~~cm.~~	contracted	179
L calf	202	~~cm.~~	R calf	208
L arm length	467	~~cm.~~	R arm length	453
L leg length			R leg length	
A.	512	~~cm.~~	A.	516
B.	568	~~cm.~~	B.	572

c. Thorax and spine

Closely related to the measurements of extremities is the asymmetry of the thorax and the lateral curvature of the spine (scoliosis). Kuchenmeister recommended the use of a special tape measure having zero at the center and reading outwards to both ends: the zero to be held at the spinous process (of the 5th Dorsal vertebra in this series) and the ends to meet anteriorly in mid-sternum (at the level of the 2nd rib in this series). Kuchenmeister gives the following report from Wintrich:

---

measurements in sixteenths of an inch. A leg length= anterior superior iliac spine to lateral malleolus; B leg length = trochanter to lateral malleolus.

R handed have 0.5 - 2 cm. more in R half of thorax than in L half

L handed have 0.5 - 1.25 cm. more in L half

"Die Differenz schien mir ubrigens links mit einem Plus nicht so gross zu sein als rechts mit einem Plus (Leber? etc.)"

Kuchenmeister declared that too much emphasis has been placed on handedness as a cause of difference in the two halves of the chest. The three lobed lung normally found on the R should be considered as a cause of some of the usual R-sided size asymmetry. Further, it must be borne in mind that pathological conditions may cause profound alterations in the size of each hemithorax. The degree of curvature of the spine, if it exceeds that usual in situs solitus, must be considered.

Lovett (381) found 90% of cases of postural scoliosis in children with the concavity on the R, the R shoulder low, and a vertical twist of the shoulder girdle in relation to the pelvis such that the R shoulder rotated backward while the L shoulder rotated forward. (Is there a definite relation to handedness? Newman (372) finds: "apparently about <u>eighty per cent</u> of single individuals are definitely right-handed".) Gruber (348) according to Arneill, found curvature of the dorsal portion of the spine mentioned in case reports of SIVC 11 times: 7 cases curving to the L and 4 to the R. Unfortunately very few modern authors have observed this feature.

Herzbruch (355) reviews several opinions on the cause of physiological or postural scoliosis. Gruber and Bährıng attributed it to the position of the aorta. Its normal position on the L of the vertebral bodies causes

a declination to the R by reason of its pulsation (giving concavity to the R in situs solitus). Richat and Becard claimed that the scoliosis depended on handedness, the stronger back muscles being on the same side as the stronger arm and therefore causing curvature with concavity on that side. However, Herzbruch concludes that the handedness explanation is insupportable because:

in 22 cases the curvature was observed to be:

8 cases to R or no curvature
13 cases to L (8 of which were R-handed)
1 case no data

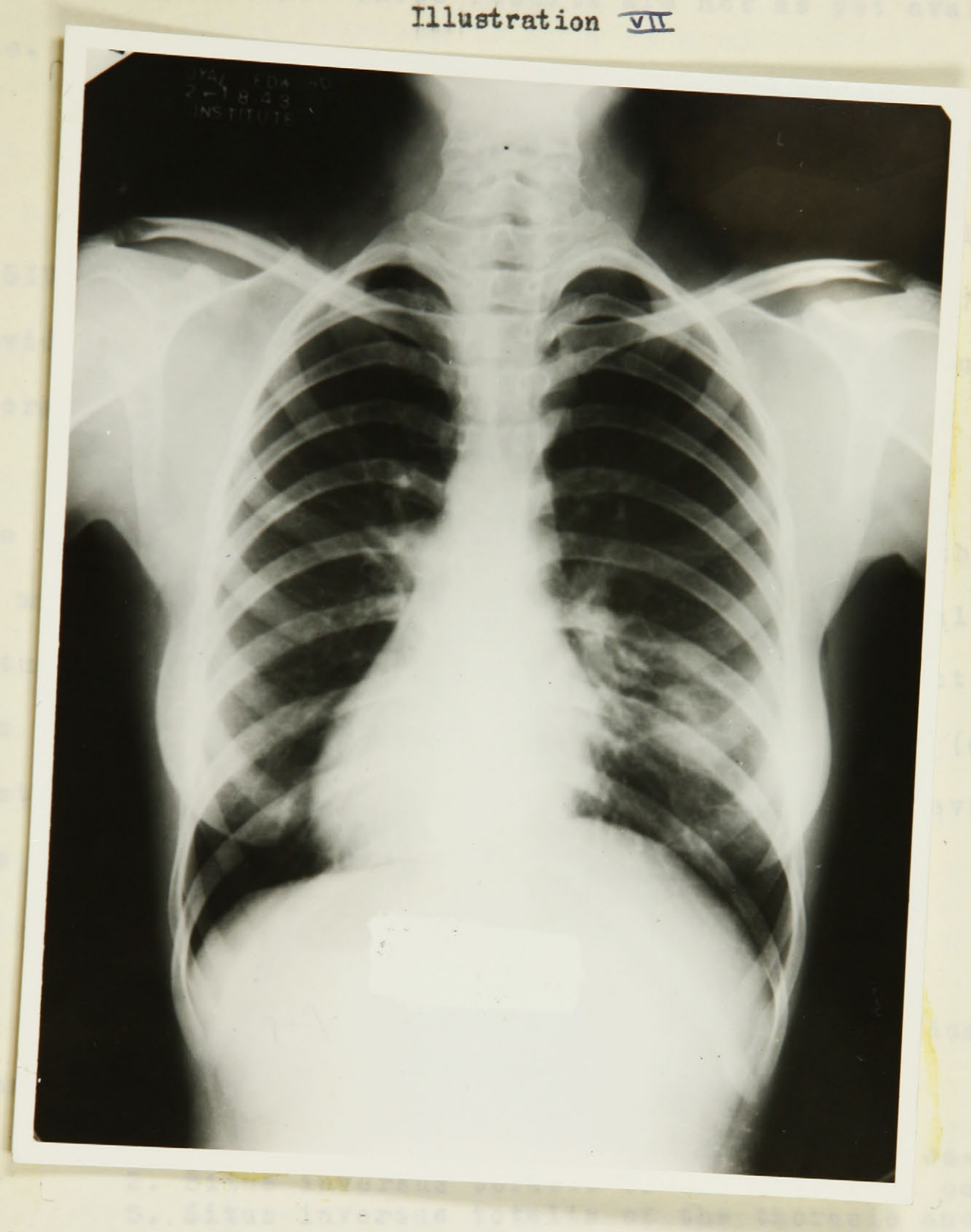
and only 1 case in 22 was L-handed

d. Breasts

Very closely related to handedness and measurements of the extremities is the question of breast asymmetry, more noticeable in the female. The left breast is usually larger. Pieraccini (403) has explained this on the basis that the L posterior intercostal arteries are shorter than the R and therefore closer to the heart, and that consequently the flow of blood to the L breast is at a greater speed and pressure. Linked with this is the greater development, in R-handed persons, of the R half of the pectoral girdle. Since the blood supply of the breast (axillary, intercostals, internal mammary arteries) is partly derived from the subclavian artery which supplies the shoulder and arm, it is logical (following the argument of Pieraccini) to suppose that the breast on the side of the less active arm would receive more blood.

Observations on female breast asymmetry in SIVC have not come to the author's attention. In his cases an

Illustration VII



Chest plate of D.K. Case V

Dextrocardia is demonstrated. The R breast shadow reaches down to the junction of the shadow of the posterior portion of rib 9 and the anterior portion of rib 7. The L breast shadow reaches down almost to this level, but there is a triangular clear space between the breast shadow and this junction. This suggests that the R breast is larger. The gas shadow in the transposed stomach is not well reproduced. (Courtesy of Royal Edward Institute, Montreal).

attempt to obtain photographic evidence on this matter is being made; 4 of 6 cases are female, but only 2 of the 4 are beyond puberty. These results are not as yet available.

3. Discussion

Further elaboration of the anatomical details of SIVC is not in place here. Cleveland's paper (5/) provides excellent details of the internal disposition of organs.

Under diagnosis (cf. page 13) the statement was made that the R side of the face, the R breast, and the L arm might be found to be larger than the contralateral features. From the foregoing discussion it is evident that reliance must not be placed on such observation (at least until more data have been gathered) as direct evidence for the diagnosis of SIVC.

4. Partial transposition

Herzbruch (355) gave the following classification (from Mosler) of situs inversus:

1. Situs inversus totalis of the thoracic cavity
2. Situs inversus totalis of the abdominal cavity
3. Situs inversus totalis of the thoracic and abdominal cavities
4. Situs inversus of single organs of one or other half of the body.

#"Am häufigsten ist der Situs inversus totalis der Brust- und Bauchhöhle. Gruber hat die Häufigkeit auf 75% angegeben, während auf die drei anderen Arten nur 25% fallen."

Killinger, (367) eighteen years afterward, classifies situs inversus:

Translation: "Situs inversus totalis of the thoracic and abdominal cavities is the most common. Gruber gives 75%for the frequency of this type, leaving only 25% for the other three types."

1. complete
2. heart only
3. all viscera except the heart.
4. complete or incomplete with associated defects

Killinger's classification is open to much criticism and indeed might serve as the basis for a protracted discussion on the etiology of transpotition. There are those who believe that visceral transposition arises in at least two ways: with and without associated defects - the former being a genuine malformation due to defective germ plasm and the latter being something different which is explained as more pardonable developmental error.

Hickman (355a) reports complete situs inversus of all viscera including blood vessels, excluding only the heart itself. The case of Royer and Wilson (413) is cited as an example of Killinger's type 3. This may be objected to on the ground that his case might better be regarded as complete SIVC with CHD, therefore Killinger type 4. This latter view is supported by the following additional stigmata of teratological development found in the report.

1. multiple spleens (5)
2. clinical signs of CHD:
   poorly developed, barrel-chested, pot-bellied
   cyanosed lips, conjunctivae, tongue and mucous membranes
   loud blowing systolic murmur
   clubbing of fingers and toes
   red blood cells 8,540,000 (in a 6 year old)

The case of Clemente (99) is likewise supposed to be Killinger type 3, (article not available at McGill). Lichtman (158) remarks "Even in complete situs inversus the heart must be demonstrated on the right side. Cases occur with situs solitus of the heart".

There are numerous examples of Killinger's type

1 and 2 and Herzbruch's type 1 and 2; these will not be mentioned here. Of more interest, preliminary to a discussion of etiology, are the examples of Herzbruch type 4. Foggie (337) referred to a case by Mollenbrock# with only the stomach (dextroposed) transposed. He stated "there are also not a few transition cases, such as the one mentioned by Abernethy (304a) in which there was, along with an almost complete inversion of the thoracic organs, a liver situated in the middle line"! Bujalski (Kuchenmeister case 59) reported a case where only the stomach and duodenum maintained the normal position for situs solitus. Blegny and Baux (Kuchenmeister case 10) found the stomach under the transposed liver. Royer and Wilson (413) state that someone has reported a case in which the gall bladder was found under the R lobe of the liver (which, in SIV would mean failure of transposition of the gall bladder as in McCrae's 49 day child, above).

Undoubtedly the classification of many reported cases depends upon the amount of study given to the anatomical details. Royer and Wilson give the rule that transposition of the lungs generally means SIVC. Although they consider their own case an exception to that rule, it has been indicated above that it need not be so considered. For clinical guidance in using this rule, laryngoscopy or lipiodol visualization of the bronchi may be employed. Further detailed review of all recorded cases may reveal sufficient evidence to establish as truth

This case has not been located as yet. It may be the case reported in Kuchenmeister (Case 6, by Mollenbrock, V.A. in 1671) because that 20 year old female is reported to have "Magen rechts", CHD, but normal position of the lungs.

the present author's hypothesis that the variants of situs can be arranged in a continuous series from situs solitus to SIVC.

Lichtman (158) in writing on dextrocardia has some noteworthy remarks concerning differential diagnosis of the various types of transposition. "By the term 'isolated' dextrocardia is meant heterotaxia of the heart alone with normal position of all other viscera....'complicated' or uncomplicated depending on whether cardiac malformations accompany the anomalous position of the heart." Concerning demonstration of lung inversion by bronchography or bronchoscopy, Lichtman writes that in the absence of normal variation, the relations of eparterial bronchi and the number of pulmonary lobes will provide the diagnosis. Depression of the right leaf of the diaphragm rules against acquired dextroposition of the heart, and it is present in both complete and isolated dextrocardia. Consequently one can not infer from a lower position of the right leaf (than the left leaf) that the liver is transposed. Finally, as regards help given by electrocardiography, he insists that inversion of Lead I is not pathognomonic of mirror-picture dextrocardia since inversion of heart chambers may occur in situs solitus.

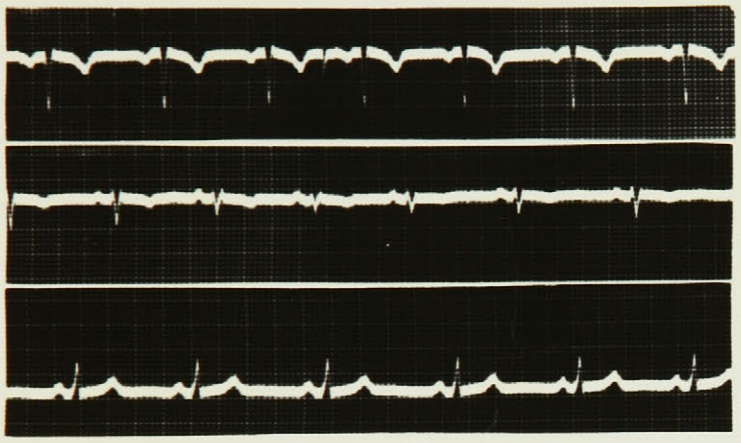
F. Physiology of SIVC

1. Cardio-vascular system

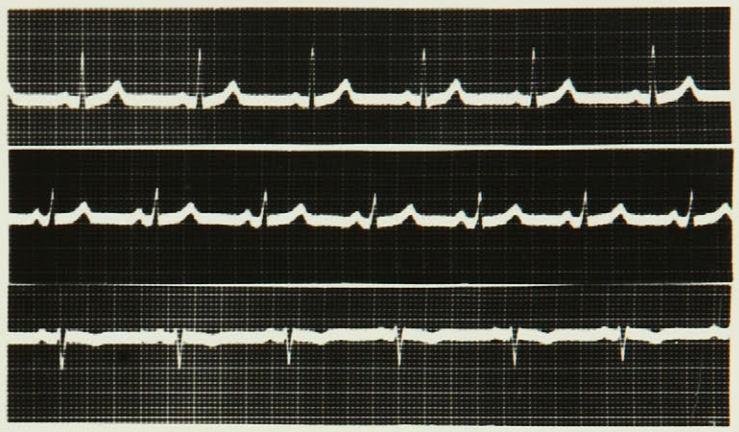
a. Pulse

The argument of Kuchenmeister that a bilateral difference in the force of the pulse felt in carotid, ulnar, radial, etc. arteries, may be palpated will not be

Illustration VIII



Mrs. M. Y. R.V.H. M.O.D. 9087 Normal Leads



Mrs. M. Y. R.V.H. M.O.D. 9087 Reversed Leads

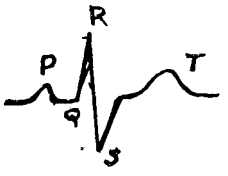
EKG of M.Y. Case II.

Dextrocardia of SIVC shown by complete inversion of I, and the interchange of II & III. Note the effect of exchanging R and L arm electrodes- a normal EKG is produced. (Courtesy of Department of Medicine, Royal Victoria Hospital, Montreal).

objected to by the present author. It can be explained presumably on anatomical grounds and may be anticipated only when there is no complicating cardio-vascular anomaly accompanying the true dextrocardia and transposition of the great vessels. Unquestionably a mechanical means of detecting the bilateral difference would (in the light of the extensive work in instrumental sphygmology of Marey, von Kries, von Frey, Roy and Adami, Oxanam, and Fick, and the research in tactile sphygmology of Ewart, as reported in the latter's book (334) lead to more satisfactory results. However, this evidence of transposition is of much less significance clinically than that which follows.

b. Electrocardiogram

The usual leads employed in making electrocardiograms are:



Lead I	R arm	L arm
Lead II	R arm	L leg
Lead III	L arm	L leg

The normal electrocardiogram is made up of waves known as:

P wave	auricular contraction; P II is greater than P III
QRS complex	spread of impulse through Purkinje network of the ventricles; I and III usually larger than II
T wave	end of ventricular systole, I is smaller than II; III is smaller than II

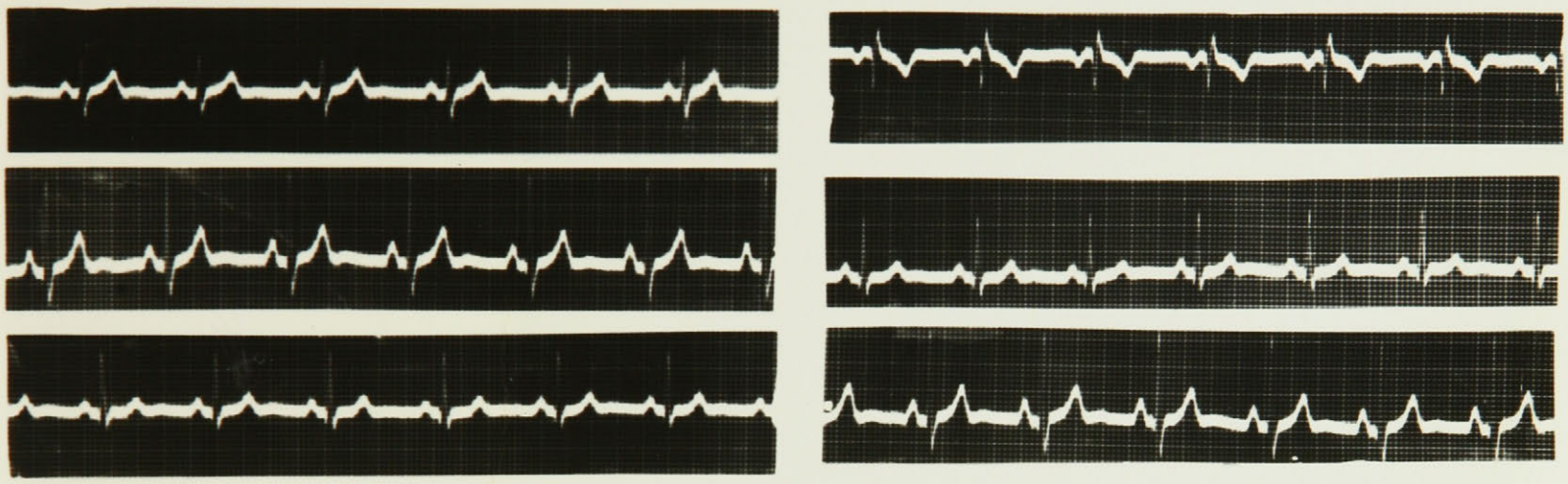
By inspection of these waves one can learn to recognize the tracing of a normal sinistroposed heart.

By means of EKG Drs. Abbott and Meakins (304) provided a method for the differentiation of acquired dextroposition of the heart from congenital dextrocardia; for the differentiation of mirror-picture dextrocardia from a

"dextrocardia due to embryonic arrest". So far as has been determined, these authors were the first to employ reversal of electrodes as an aid to differential diagnosis in these cases. Smith and Horton (422) however, emphasize the technique far more, twenty-one years later in a paper devoted to this alone..."in making the electrocardiogram, the right arm wire, which is normally nearer to the auricles and the basal part of the ventricles than to other parts of the heart is now, because of the transposition of the heart, nearer to the apical part of the ventricles. The left arm wire, instead of being nearer to the apex, is now nearer to the base of the heart. In hearts developmentally transposed, the currents develop normally, but owing to this different leading off from the heart to the galvanometer, the tracing of lead I is turned upside down, that of lead II is the ordinary standard lead III, and that of lead III, the ordinary standard lead II". (Cf. Illustration VIII).

Taussig (429) presented a thought-provoking paper on the anatomy of the heart in SIVC, showing that the muscular architecture (studied after the methods developed by Mall, following MacCallum whose unfinished, brilliant work he completed) is altered. The "superficial muscle bundles of the ventricles were not a mirror-image of the normal, but.....their direction was essentially the same as that of a normal heart.....ran spirally from base to apex in clockwise direction.....immediately upon peeling off the thinnest possible superficial layer one came upon a deeper muscle layer which ran at right

Illustration IX



Mr.J.P. R.V.H
Dextroposition (Tbc)

Normal leads Reversed leads

EKG of J.P.

An essentially normal EKG although the heartis dextroposed, as shown by the x-ray(Illustration III). Note the effect of exchanging R and L arm electrodes now is the production of the picture of dextrocardia(now with reversed leads whereas it was seen in the case of M.Y. with the normal leads). (Courtesy of Department of Medicine, Royal Victoria Hospital, Montreal).

angles to the superficial layer.....the outer part of the middle layer of heart muscle has been repeatedly demonstrated to lie nearly parallel to the superficial muscle layer." Her findings were identical in two hearts examined, from patients diagnosed as SIVC at autopsy. One might expect, since the musculature (at least the Purkinje fibers) is directly involved in the origination and the conduction of the electrical phenomena, that mirror-imaging of the "main gross anatomical structures and the deep muscle bundles of the ventricles" could account for the altered EKG picture. However, it is worthy of note, not only in this connection, but also as regards theories of etiology, that the direction of the superficial muscle bundles is unchanged! Taussig cites Davis (Carl L. Davis in a 1923 publication) for the statement that the outermost muscle layer is formed earlier than the deep muscle layers. This may be an indication (the similarity in direction of outermost fibers in the heart of normal and transposed situs) of the time of action of the developmental factor producing transposition.

The illustrations show an EKG of a person with SIVC taken with the usual leads and a second EKG of the same person taken with reversed leads (R arm and L arm terminals reversed).

Lead I	L arm	R arm
Lead II	L arm	L leg
Lead III	R arm	L leg

For contrast, the EKG of a case of dextroposition caused by chronic fibro-ulcerative tuberculosis is shown, using normal and reversed leads. The chest showed visible pul-

sations in the 4th R interspace in the midclavicular line. This illustrates that mere shift of cardiac position is not sufficient to account for the diagnostic alterations in the EKG.

c. Lateral dominance and the cardio-vascular system

Hyrtl (57) believed that handedness and other phenomena of lateral dominance could be explained on the basis of anatomical variations in the blood supply of symmetrically disposed organs. The normal blood supply to the R arm arrives under greater pressure and in greater volume than that to the L arm because the origin of the R subclavian is in a straight line from the L ventricle, whereas the origin of the L subclavian is further from the L ventricle and blood reaches it after pursuing a course with double angulation. Hyrtl observed individuals with certain vascular anomalies which provided the L arm with a greater blood supply than the R and found that they gave a history of L-handedness or showed at autopsy (by evidence of greater muscular development of the L arm or greater callousity of the skin of the L hand) that they were L-handed. On the basis of this theory all persons with SIVC should be L-handed. Hyrtl's theory is sound as far as it goes. It does not and need not explain R-handedness in an individual with SIVC who has been trained to overcome L-handedness (consciously or unconsciously as in Case I, below). It cannot explain certain cases of L-handedness, however, which persist despite training toward R-handedness, in the absence of any vascular abnormality.

The role of cerebral dominance in relation to handedness is also treated in Hyrtl's theory. The L side

of the brain receives a better blood supply than the R inasmuch as the L carotid is a direct branch of the aorta while the R carotid is a branch of the smaller vessel, the innominate. The greater frequency of embolic phenomena in the L side of the brain, and observation of Hyrtl upheld by modern pathologists (Boyd), supports this concept. Wile (436) cites O'Connor (395) who strengthened Hyrtl's hypothesis by showing that the vertebrals also contribute more blood to the L than the R side of the brain. However, Wile and the others criticize Hyrtl's idea by drawing attention to the free circulation within the Circle of Willis and declaring that this obviates the possibility of any part's receiving more blood than any other.

2. Central Nervous System

a. Localization unilaterally of bilateral functions

"It is agreed that the speech zone is on the left side of the brain in right-handed individuals and on the right side of the brain in left-handers. In exceptional cases (possibly unrecognized left-handers or uncrossed pyramidal tracts) a right sided lesion may give symptoms of aphasia.....generally, if a lesion is in or near the cortex in the speech zones aphasia is sure to result." (Wechsler, 433 page 328) It may be that the speech center in Case I (L.H. whose bilaterally R and bilaterally L head photographs were included above to show the R side to be larger than the L) is on the R side despite evident R-handedness.

Some authorities believe there is a unilateral

localization of function in certain parts of the peripheral nervous system. In line with this belief the R splanchnics are sometimes severed for the relief of intractable bilateral or midline visceral pain. (Should one then sever the L splanchnics in SIVC?) Certainly this is one of the least understood matters of all that relates to SIVC. King (139) in reviewing cases of appendicitis in individuals with SIVC hypothesizes that there are cases in which the situs of the nervous system does not correspond with that of the viscera. Indeed he believes that the mechanisms for inversion of the viscera and the nervous system are independent. This is King's way of explaining the frequent observation of surgeons that the maximum pain and tenderness in L sided appendicitis of SIVC was on the R side.

Granted that unilateral physiological dominance does occur in the central nervous system, it remains necessary to prove that it occurs peripherally. King cites experiments by Jones on distention of the gastro-intestinal tract by balloons: small areas of localized pain in the abdominal wall were caused, most of which were in the midline; but distention of the caecum caused maximum tenderness at McBurney's point. This, together with observations that retrocecal, pelvic, and even sinistroposition of the appendix still causes maximum tenderness at McBurney's point, leads King to conclude that there is an asymmetry of the nervous supply to the gut. #

However the author has recently observed the case of a woman admitted to the gynecological service of the RVMMH with LLQ pain of a very severe character, caused by a

Evidence from many sources tends to demonstrate the bilaterality of the nervous system in anatomical and physiological features. The innervation of the gut is provided while the latter is still a midline organ (per sonal communication from G.L. Streeter in King's paper). Consequently one would expect the nerve supply of all parts of the gut to be bilateral. (This is upheld by the observations of Wrork (437) who found that, contrary to popular teaching, the splinting of abdominal musculature is of no diagnostic help in lateral localization of intraabdominal disease. Wrork used a mechanical muscle tensionometer to compare the degree of splinting bilaterally.) Unless there be asymmetry in the peripheral nervous system, "transposition" of the peripheral nervous system is meaningless.

b. Lateral dominance

Although no one is fully prepared to state in what way R-handedness, R-eyedness, L-brainedness, etc. are related to situs solitus, much important experimental work has been done on lateral dominance, and tests have been devised which enable one to diagnose R and L sided dominance. Consequently the present discussion of this question (will be brief and) is intended to indicate a possible method of approach to the answer to this still unsettled question. If proper tests on lateral dominance were employed in numerous cases of SIVC, it would soon

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R-sided appendix stretching across the midline into the LLQ. This instance supports the opposition to King's conclusions by revealing again that localized tenderness from the exact position against the parietal peritoneum of the diseased viscus does (at least) sometimes occur.

become apparent whether visceral situs and various types of lateral dominance were related.

The interrelationship of eyedness and handedness is denied by experiments of Peterson (399) and others cited by Jasper and Raney (360). In the same paper, Jasper and Raney evaluate motor lead preference in simultaneous movement as a test of lateral dominance, concluding that the test is frequently unreliable. However, in a subsequent paper (361) these authors report an apparatus for the determination of unilateral dominance in the central aspects of the visual-perceptive system; and this they consider to be 90% reliable. Other tests for lateral dominance are likewise discussed. Gayda (343) reports bilateral differences in the reflex time of the knee jerk in man, measured instrumentally. His explanation for the shorter reflex time of the L knee jerk in R-handed people depends on the theory that the cortex contralateral to handedness is better developed and consequently exerts an inhibitory influence to spinal reflexes on the side of handedness. This inhibitory influence increases reaction time. If Gayda's apparatus and his results are easily reproducible, this may indeed prove to be a useful test for lateral dominance.

c. Electrical phenomena of the brain

Three reviews (331, 359,) cover the literature on the electro-physiology of the brain and spinal cord from its beginnings through 1938. An electroencephalogram is a record of the electrical activity of the brain as recorded through the intact skull and scalp, by means of electrodes which may be fastened to the skin

Illustration X

Case No. ..... **MONTREAL NEUROLOGICAL INSTITUTE** E.E.G. No. .....

E. E. G. REPORT

Name Mr. L.H. Age ..... Ward ..... Time ..... Date April 17th, 1942

Object Research study

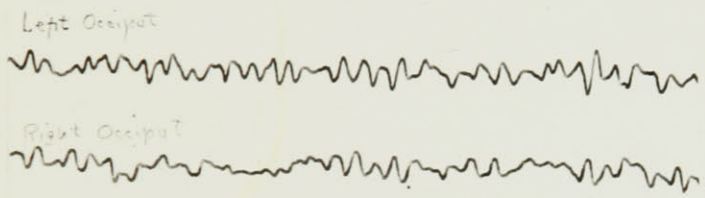
Medication None Pre-Op. x Post-Op.

Gen. Cond. ment. emot. state coma, aphasia, etc. Good cooperation

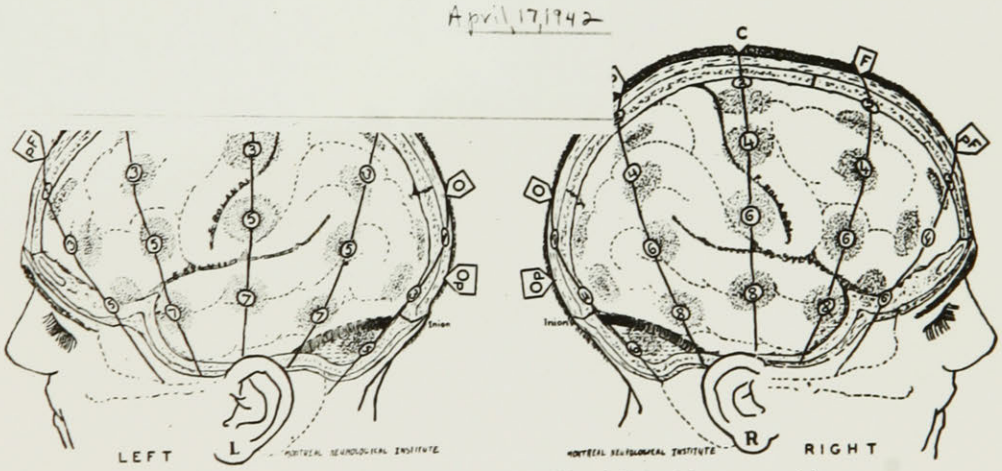
Alpha rhythm was more continuous from the left than on the right occipital region. Since this rhythm is blocked with sensory stimulation, such as by opening the eyes, it may be assumed that its amount is inversely related to cortical excitation. Hence the average excitatory level of the right is higher than that of the left. This is the converse of that observed from thoroughly right handed individuals but comparable to that of left handed individuals.

H. Jasper

Dr. H. Jasper.



April 17, 1942



Delta Waves from area in Black:—Spikes and Sharp Waves in Red:—Quiet area open circle

EEG of L.H., a R-handed person with SIVC. Case I

(Courtesy of Dr. H. Jasper, Montreal Neurological Institute)

with adhesive. There is in general a tendency to individuality and to reproducibility of pattern under standard conditions (331). The pattern of electrical activity alters with physiological and pathological states, in a diagnostic fashion.

Raney has published two papers (404,405) of particular significance in the present discussion. These concern lateral dominance and the electroencephalographic findings in identical twins. It is important, first of all, to learn that electroencephalography can provide another method for diagnosing laterality. "Upon examining the electro-encephalograms, it is evident that there are significant differences in the electrical activity of homologous regions of the right and left hemispheres." (405)

Included herewith are records from Case I (L.H.) showing the bilateral differences, interpreted by Dr. Jasper as indicating greater activity (or dominance) of the R cortex. This is in keeping with the observation, above, that the R half of the face is larger, with his history of having been L-handed until trained in school to prefer the R-hand.

It would be of great theoretical interest to obtain EEG tracings on the monozygotic twins reported by Cockayne (53). The twins of Raney (405) were presumably all situs solitus individuals and yet "there is a tendency for one twin to show bilateral differences which are the reverse of those found in the other twin". What then would Cockayne's twins (one being SIVC, the other

being situs solitus) show?

d. Obstetrics

Beck (314) gives the frequency of various modes of delivery as follows: vertex, 96%; breech, 3%; face, 0.5%. He further states that 70% of the vertex presentations are left occipito anterior (LOA) and only 10% right occipito anterior (ROA). Beck explains that the fetus accomodates itself to its environment - the smooth dorsum of the passenger fitting the anterior portion of the uterus, and the irregular outline of the fetal extremities adapting well to the posterior part of the uterus which is indented by the vertebral column - the best adaptation being responsible for the most frequently observed relation of fetal and maternal parts. The greater frequency of LOA (the fetal occiput in the left anterior quadrant of the maternal pelvis) is attributed to the presence of the sigmoid colon in situs solitus, on the left side, and "the fact that the uterus usually undergoes a torsion toward the right side" (Beck, >14 page 106).

With the last two visceral factors altered in SIVC, one would naturally expect the frequency of LOA and ROA to be reversed. Observations on this matter would at least serve to test the validity of the explanations for the frequency of the various positions. The one reference to this matter found in the literature (has been misplaced) relates the delivery of a woman with SIVC by the ROA mechanism. Case II in this series (M.Y.) bore ten children, but the deliveries were at home and records are therefore not available.

Lactation brings another evidence of normal physiological asymmetry which is probably reversed in SIVC, again for anatomical reasons, if the observations of Pieraccini (463) are correct. He found that the human L breast normally secretes more milk than the R. (His explanation has been given, page 52 above.)

G. Pathology

1. Kartagener syndrome

Including the cases first described by Kartagener in 1933 (136) there have been about two dozen observations reported of the occurrence of a clinical triad which has come to be known as the Kartagener syndrome. It consists of sinusitis, bronchiectasis, and SIVC. With the exception of the case of Newns (200) the references can readily be found by title in part I of the reference list for this thesis. There are other reports which suggest that the patient had this condition. Identification of either sinusitis or bronchiectasis may at times be a difficult matter. Rosenthal (234) recommends lipiodol visualization in all cases of SIVC and explains that the identification of bronchiectasis is more certain by lipiodol during life than by direct anatomical examination after death.

Adams and Churchill (4) found the incidence of bronchiectasis in 232,112 admissions to the Massachusetts General Hospital to be 0.306% in persons with situs solitus, and 21.7% in 23 persons with situs inversus. They remark: "there may be two types of individuals with transposition of viscera- first, completely normal mutants

and second, true monsters in whom other stigmata of maldevelopment may be anticipated; the inference is that the bronchiectasis in these cases is to be regarded as a stigma of maldevelopment". Adland and Einstein (5) express similar views, but also refer to Kartagener's explanation for the greater incidence of bronchiectasis in SIVC: general lowered resistance of the body. Such an explanation requires the support of a group of facts showing that visceral transposition lowers bodily resistance - evidence which has not been published.

2. General pathology in SIVC

Gruber (349) is reported by Arneill (303) to have concluded that transposition has no effect on longevity or the cause of death. This statement was based on the study of the seventy cases reviewed by Gruber, and it was upheld by Kuchenmeister after his review of 149 cases. The cause of death in reported cases, as reviewed by the present author, is not confined to any organ system, organ, or tissue, and varies as widely as in the general population. A similar survey of the complaints bringing these patients to their physician, demonstrates that they manifest no particular susceptibilities to diseases.

Several reviews have been made of reported cases to enumerate the different congenital anomalies found in conjunction with SIVC. Karsner (365) reviewed Kuchenmeister's cases:

1.	Valleix	CHD
2.	Liebermeister	CHD
3.	Winter	CHD
4.	Schrotter	CHD
5.	Boyer	persistent ductus arteriosus
6.	Juli	undescended L testicle
7.	Hickman	accessory spleens

8. Kahlkoff	16 small spleens, congenital umbilical hernia, absence of Spigelian lobe of liver
9. Dauberton (Sue)	absence of R kidney
10. Herboldt	congenital cystic kidney

Additional cases from Kuchenmeister are as follows:

Cooper (K#72)	CHD
Gamage (K40)	CHD
Mollenbrock (K6)	CHD
Abernethy (K29)	spleen in 7 parts
Baillie (K26)	3 spleens
Delamare (K22)	spina bifida
Heuermann (K19)	bilobed lung bilaterally

Ballantyne (308) lists the following:

Jellett	CHD
Vincenzi, L.	CHD
Whinnie	union of superior and inferior venae cavae before reaching heart
Marchand	splenic anomaly
Launay	" "
Hyrtl	" "
Beaufume and Caron	absence of R kidney and suprarenal capsule
Pic, A.	thymus gland persisting at 35
Boyd	bifidity of thumb
Fraser	" " "

Fraser states that his case (338) is the same as that of Boyd (316) although apparently Ballantyne overlooked this in preparing the list.

Herzbruch (355) mentions three anomalies:

Weisflog	hydrocephaly
Schartan	hydrocephaly
Valleise	harelip

There are many more. Of Dubreuil-Chambardel's twins (75) with harelip there will be discussion below. Karsner's own case suffered from hemophilia and showed at autopsy agenesia of the L kidney and ureter with undescended testicle on the same side. Lane reported a man with R clubfoot.

Kuchenmeister's case number

Apparently there is no peculiarity about the type of associated anomaly found in SIVC. CHD is frequent - but there is some question whether observers are not more apt to notice or report this (and certain other anomalies) than defects which have proven less interesting to the medical profession.

3. CHD in SIVC

Individuals whose SIVC is discovered at autopsy are more apt to be reported if they show some associated anomaly which seems in itself sufficient reason for the preparation of a paper. Such a condition is CHD. Likewise, individuals, although aware of a dextroposed heart because of its pounding on the R side of the chest on exercise, are more apt to seek medical attention if additional symptoms of CHD are manifested. It is no wonder, then, that CHD is so frequent in the reported cases of SIVC. There are 22 new references of SIVC with CHD since Cleveland's review: (16, 2, 35, 48, 50, 67, 73, 80, 103, 104, 109, 161, 180, 200, 202, 214, 215, 227, 228, 234, 263).

There is no preponderance of one type of CHD in the list of references just given. It is true that Roger's disease and three chambered hearts occur several times in the series - but not in greater relative frequency, for example, than in Dr. Abbott's series of 1000 reported in Nelson Looseleaf Medicine.

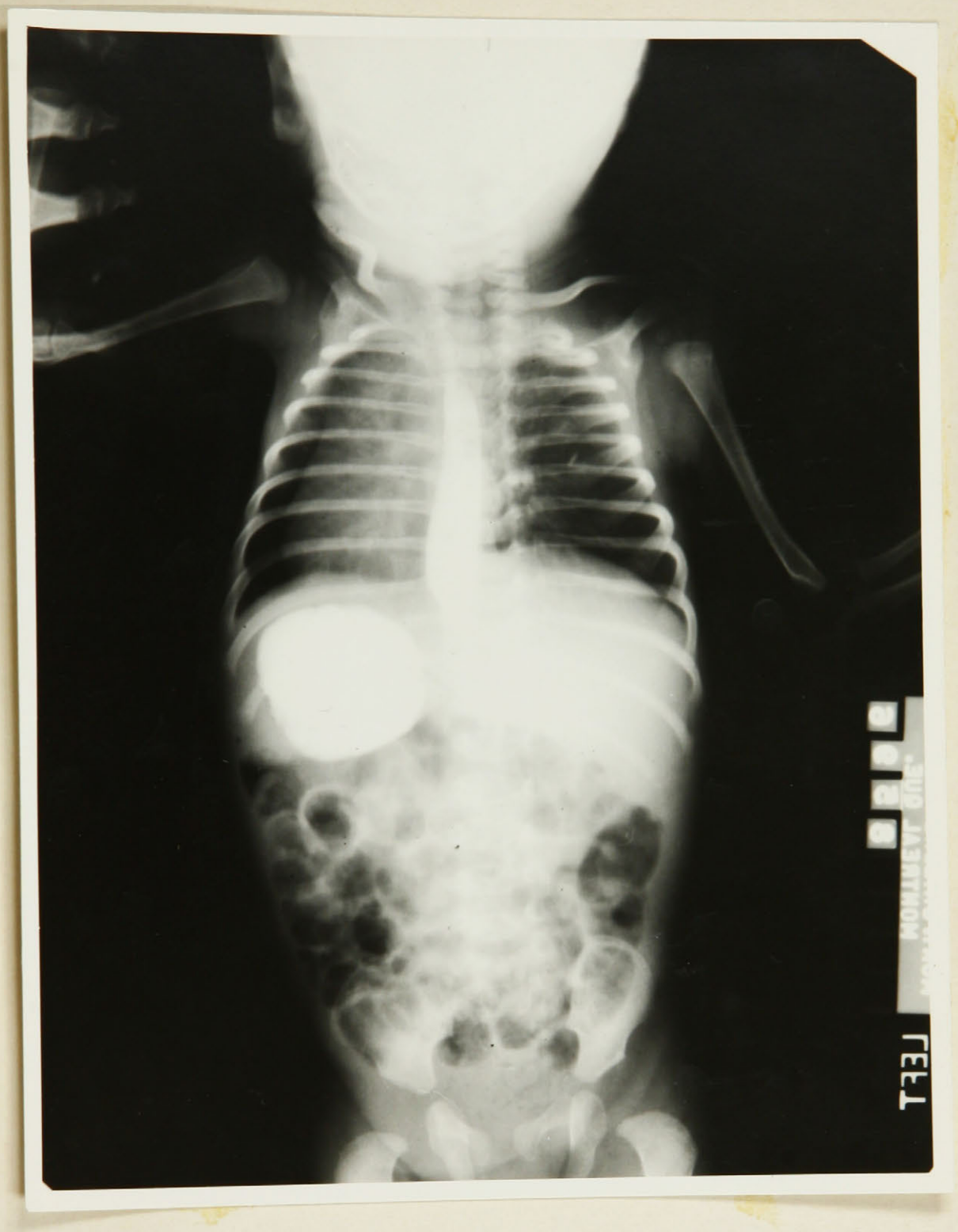
4. Cryptorchidism in SIVC

Karsner writes as follows: "Perls claims that in situs inversus undescended testicle is fairly frequent at birth, but descends either in the first year or at pu-

berty. Kuchenmeister (page 190) says that in 80% of cases with situs solitus the testicle is descended at birth and of the remaining cases, 12.2% show retention of the left and 7.8% retention of the right. The presence of an undescended testicle predisposes to hernia because of the fact that in such cases the processus vaginalis is likely to remain more or less patulous until complete descendis occurs." (365)

The case of Juli, quoted by Karsner, is listed above. Karsner's case was another. Case III (J.A.) of this series was born with cryptorchid condition bilaterally as reported in case history No. 18,842 at the Children's Memorial Hospital, Montreal. However, upon examination at 10 months, the author found the testes in the scrotum bilaterally. Thus, as Perls claimed, undescended testicle was found at birth but corrected within the first year of life.

Illustration XI



X-ray of J.A., thorax and abdomen. Case III

The barium drink is seen in the esophagus and stomach. The esophagus, more to the L than to the R in situs solitus, is here seen to the R of the midline. The stomach is dextroposed and the liver is in the L hypochondrium. The heart shadow is visible in the R hemithorax. (Courtesy of Montreal Children's Hospital).

V.

ETIOLOGY

A. Theoretical considerations.

In a previous section was given the history of theories on the etiology of SIVC up to the present century. In this century the notable development of genetics has made it possible to include with the others (as was also shown above) a theory of a hereditary origin. In the following discussion, the ideas still surviving in the twentieth century will be divided into hereditary and environmental causes.

On the basis of ideas about teratogenic factors, gathered from many sources (with most help from Ballantyne), the following outline of possible hereditary and environmental factors is offered: (cf. Table III, page 73).

This table is worthy of study in the light of several general theories of teratogenesis, about to be discussed. For example - the theory of developmental arrest may be invoked almost throughout the table, because if it be true that extra-genital maternal traumatism can cause spina bifida or anencephaly (Ballantyne, pages 302 and 137), it may produce it by temporary developmental arrest. On the other hand, it may be true that faulty placentation will sometimes produce spina bifida (a theory supported by Dr. W.V. Cone of the Montreal Neurological Institute), by developmental arrest; and faulty placentation may be an inherited trait. Dr. J.R. Fraser (Royal Victoria Montreal Maternity Hospital) explains (to his students) that a few

TABLE III

Possible Etiological Factors

A. Maternal Impressions

Only insofar as the state of mind during gestation (more especially the early part) can affect the vascular and nutritive supply to the embryo. (Ballantyne, 1905)

B. Pressure

1. Extra-genital maternal traumatism (process of contre-coup
   a. more likely if oligohydramnion
   b. cause wounds, fractures, dislocations

2. Abdominal traumatism, genital
   a. long continued and not excessive, or
   b. short, sharp, severe
   c. action: 1) directly crushing or wounding embryo
      2) cause morbid state uterine walls, placenta, amnion

3. Intraabdominal and intrapelvic
   a. tumors
   b. pelvic contraction (malformed)
   c. uterine narrowness or contraction (malformed)

4. Intrauterine
   a. tumors
   b. multifetation
   c. pressure parts embryo against one another
   d. funic pressure (cf. below)
   e. amniotic bands; amniotic pressure (cf. below)
   f. placenta praevia and other faults of placentation

C. Inheritance ("pathology of the germ")

1. single anomalies (harelip, polydactyly) (child)
2. multiple anomalies (dysostosis cleido cranialis) (child)
3. uterine abnormality inherited (mother)
4. placental abnormality inherited (placenta)
5. mutations germ by roentgen-therapy (father or mother)

D. Maternal Health and disease

1. toxemia; drugs
2. roentgenotherapy
3. infectious disease
4. intrauterine fetal inflammation (B.F. Davis, 1915 Am. J. Dis. Child)
5. disease of fetal membranes (cf. amniotic bands below)

E. Twins and monstrosities (cf. also B4 above)

1. anastomsis placental circulations; malnutrition of one
2. developmental arrest; formation new organizing centers

F. Birth order and maternal age
   1. parental age difference
   2. primigeniture
   3. last born
   4. father younger than mother
   5. mother over 40

G. Funic pressure
   1. pressing one part fetus against another
   2. surrounding parts to cause amputations

H. Amniotic bands, etc.
   1. disease of amnion (adhesive bands formed following inflammation also)
   2. pressure of amnion
   3. arrested development of amnion

ectopic (tubal) pregnancies may be due to abnormally rapid development of the fertilized ovum, so that instead of being ready for implantation on the eighth or ninth day (four days, it is thought, are necessary for passage down the tubes to the uterus), the ovum is ready while still in the tube. Similarly, according to Dr. Fraser, some ova develop more slowly than usual and consequently they are not ready for implantation until near the internal os of the cervix, where implantation is precarious (placenta praevia in one of its variations). It is quite within reason to consider that these variations in speed of development do occur and that they may be inherited characteristics governed by factors contributed by either the maternal or the paternal germ plasm. The faulty implantation occurring then, may result in developmental arrest because of improper oxygen supply through a badly arranged placenta. In this connection, the "bilobed" placenta of Case IV is worthy of note. Exactly what was meant by "bilobed" cannot be determined because the doctor who made the note is no longer in Montreal. It probably represents the "duplex" placenta of Ballantyne (page 590); that authority writes: "their teratological significance is not obvious".

B. Developmental arrest theory

Stockard (426) gave an explanation applicable to all types of structural deviations from the specific normal. He adapted Wilder's conception (935) of a graded series of teratologic forms ranging from monstra in defectu through the complete single individual and monstra

in excessu to the complete duplication of separate twins. Stockard found in his own experimental work a single explanation for the entire series: slowing of the developmental rate. The rate may be affected by any of numerous environmental changes - more numerous as the complexity of the form of the developmental rate. The rate may be affected by any numerous environmental changes - more numerous as the complexity of the form of the developmental species increases, so that man is extremely susceptible to environment, accounting for the elaborate arrangements of the human womb for controlled developmental environment (teleology). As a result of these arrangements, the dangers of insufficient moisture, improper temperature, and trauma are effectively minimized, but the danger of inadequate oxygen supply remains and is frequently a probable cause of malformations. Improper placentation may cause faulty oxygen supply.

The type of malformation which results depends upon the period of development during which arrest occurs. Arrest of development in the blastocyst stage of the armadillo seems to be a physiological condition (i.e. normal or hereditary dominant, possibly) which permits, upon the resumption of development, the budding of three (Texas species) to seven (South American) additional embryonic primordia. Arrest of development later, as during the stage when the neural groove, lateral outgrowths, representing optic anlagen, are developing, results in less comprehensive structural alterations.

The universal rule of Stockard for producing

alterations of structure is to slow the developmental rate. This may be done by reducing the rate of oxidation (lower the temperature or decrease the oxygen supply). There are critical and indifferent periods in development. During the former, profound alterations will be effected by slowing the rate. During the latter, no change will result.

Furthermore, Stockard has shown that some embryos react differently to experimental conditions than others under the same conditions. The difference may be explained on a genetic basis: varying susceptibility. "The eggs of the trout are more inclined to develop into double individuals than are those of Fundulus."

Stockard's analysis leaves unanswered the causes of the cause. Faulty placentation may be the result of diseases of the maternal or fetal tissues (due to infectious or hereditary factors). It may also be due to variations in the locus of implantation (mentioned above) (which may be on an acquired or hereditary basis).

In summary, the developmental arrest theory postulates that "a complete stop in development reduces the rate of all parts to zero and eliminates normal inequalities. On resuming development from such a state parts that progress at a disproportionately fast rate are unable to attain such supremacy and all portions of the embryo start at about the same rate. The usual developmental balance and inequalities in rate among parts are lost and thus the typical form of the individual which actually depends upon these inequalities in rate of growth becomes modified." (Stockard, 426).

C. Relation to transposition of side, size, and defects.

Morrill (390), using trout of Stockard's experimental series, deals with the question of mirror-imaging. He finds it present in viscera of some of the double monsters but not in duplicate or monozygotic separate trout. Morrill contends that the R component (L-hand twin by Morrill's terminology), as pointed out by Eichwald, usually exhibits the visceral transposition. "An exception to this .....in the famous Siamese twins where it was Chang, the left twin (R-handed or B-component of the present paper), in whose body there were indications of situs inversus (Kuchenmeister, quoted from Bateson). This would give the converse of the usual arrangement."

Newman (397) reviews a paper by Komai (371) (which the writer has not seen in the original) on salmon embryo that brings "three important conclusions: first, that s.i.v. is 'a result of a disturbance of the normal developmental process, much as the small size and deformation themselves'; second, that incomplete twinning such as is found in the partially duplicate twins 'makes the appearance of s.i.v. easier'; and third, that the right-sided predominance of smaller size, deformity and s.i.v. is a consequence of 'a kind of physiological gradient passing from left to right of a fish embryo. The derangement of this gradient brings about the situs inversus viscerum'." He had "200 normal single embryos, 430 more or less abnormal or deformed single embryos (not twins), 502 sets of completely separate twins (united only by the common

yolk sac), and 287 sets of partially duplicate twins (double monsters) most of which consisted of various grades of anterior duplicity. This material is so extensive that statistical comparisons can be made and definite conclusions drawn therefrom".

Newman found that in human beings "there is .....a strong tendency for s.i.v. to occur in the right component of conjoined twins". He believes that mirror-imaging is "a residuum of an original left-hand gradient (or physiological superiority of the left side) of the pre-twin embryo". (342)

In this thesis a number of superficially unrelated facts regarding sidedness, asymmetry, size, defects, sex, and transposition have already been cited. Crew and Munro found the abnormality in fowl gynandromorphs more often on the R, larger, male side. Fekete and Burril, Greene, and Ivy found the L side of the mouse and rat to be more masculine. Gesell (345) reported pathological degrees of uncrossed unilateral size asymmetry (hemihypertrophy) to be more common in women and on the R side; Landauer (345) found it more common in L-handed people, in males, and on the L side. The asymmetry of unilateral massive breast hypertrophy in women apparently affects the L side more frequently. Komai, Morrill, and Newman found small size, malformation, and visceral transposition more common on the R side of fish and human double embryos. It may be pertinent here to recall vonBaer's hypothesis that situs depends on the position of the embryo in relation to the yolk sac: solitus if to the L, and inversus if to the R.

D. Twinning, mirror-imaging, and transposition.

That outgrowth of vonBaer's hypothesis, which Forster originated and which Tacke and Perls disproved, that <u>all</u> double monsters show visceral inversion in one component, probably served as inspiration for some of the work so ably carried on by H. H. Newman. In 1928, Newman reviewed various manifestations of mirror-imaging as manifested in human twins. He concluded that asymmetry reversal "expresses itself in varying degrees, ranging from complete <u>situs inversus viscerum</u> in conjoined twins to left-handedness or counter-clockwise hairwhorl in separate twins". The asymmetry reversal of some twins apparently accounts for an apparent dissimilarity of features in actually monozygotic sibs.

The present author (without sufficient grounds to present the matter as a theory) has already mentioned his hypothesis that a continuous series of variations between complete situs solitus and complete situs inversus may exist. Newman postulates a complete series of gradations between monozygotic twins that are identical in every feature and monozygotic twins that are complete mirror-images (as the case of Cockayne,[53])....but Newman is satisfied to have his extreme variants be conjoined monozygotic twins rather than separate individuals as in Cockayne's case.

"The reason why not all identical twins show asymmetry reversal in one twin is that the epigenetic establishment of asymmetry takes place sometimes before and sometimes after twinning. If it takes place before twin-

ning the twins will show a high degree of asymmetry; if it takes place after twinning the twins will both show the same asymmetry and be in other respects more alike than when the establishment of asymmetry precedes twinning; if it takes place during the twinning process the twins will show varying degrees of asymmetry reversal in one individual and varying degrees of close resemblance in physical and mental characters." (392)

Everything that in any way contributes evidence of this timing in development of the establishment of asymmetry must be seized with avidity. Mention has been made of the observation of Helen Taussig on the anatomy of the transposed heart. "In the first place, it has been shown that the first part of the primitive cardiac tube to be differentiated into muscle fibers is its outer portion, the so-called 'epi-myocardium', and that when this differentiation occurs, the substance between it and the endocardium is still undifferentiated material.....the outermost muscle layer is formed earlier than the deep muscle layers." (427) This perhaps indicates that the establishment of situs occurs sometime between the time of differentiation of the epi-myocardium (which has the same situs in untransposed and transposed hearts) and the time of differentiation of the deeper muscle layers (which have a mirror-image relationship in solitus and inversus).

A relationship between dermatoglyphic pattern and situs, whether it were a negative or a positive correlation, would probably help also to establish the time in development that asymmetry is determined. Cummins (326)

claimed "the association of variant finger print trends and handedness points to the anticipation of a functional dominance as early as the third and fourth fetal months, when the dermatoglyphics are elaborated definitely". No one doubts, however, that situs is definitely established long before the fourth month. The question remaining is whether dermatoglyphic patterns may not be elaborated definitely at an earlier date also.

Newman (392) reveals that he is particularly attracted by the theory of twinning as the cause of visceral transposition. After presenting the evidence of Komai's paper, he states that "no systematic examination of large numbers of one-egg twins has ever been made with the object of searching for possible cases of perfect or imperfect s.i.v. Were such a search made by means of x-ray photographs we suspect that not a few cases of s.i.v. would come to light". He next asserts the theory of the one-egg origin of conjoined twins to be an established fact. "From the literature describing the anatomy of still-born human conjoined twins we gather that as a rule the less well-developed component more commonly exhibits s.i.v. than does the more normal component, but there are a few cases in which the opposite is ture.....My search has not revealed a single case in which s.i.v. is expressed in both components.....When one finds instances of normal situs in one twin of a pair and s.i.v. in the other, there can be no doubt that one twin has undergone an epigenetic reversal of the genetically prospective asymmetry of the single zygote from which the twins were derived." He states that transposition is extremely rare in single

human individuals and that it is the general rule "while its absence is the exception" in one of the components of conjoined twins. When it occurs in single individuals "it is nearly always associated with other structural abnormalities, suggesting that s.i.v. is induced by growth-depressing agents".

Newman relates transposition to "minor expressions of mirror-imaging, such as those in hair whorl, ear form, palm and sole prints....." and declares that the latter have "the same general cause or causes as s.i.v. All reversals of asymmetry are probably due to growth-depressing agents and therefore are environmental".

It is quite necessary to learn something more about the time at which asymmetry is established in order to learn whether the cause of asymmetry reversal is environmental, as Newman supposes, or hereditary, as Cockayne proposes. It may indeed sometimes be one and then the other. However, to assume this double possibility without good reason is both unnecessary and unscientific.

In 1920-1, Stockard criticized Newman for his postulate that the "different extents of doubleness are .....connected with different times of origin of the condition as was suggested by Newman ('17), " showing that "every extent of doubleness in this fish series and the time of origin from the developmental standpoint is the same in each". Apparently Newman has still not retracted his postulate then criticized, for in his 1928 paper he explained "the reason.....why not all identical twins show asymmetry reversal in one twin is that the epigenetic

establishment of asymmetry takes place sometimes before and sometimes after twinning.....", and furthermore he states that the asymmetry reversal is most complete in "complete <u>situs inversus viscerum</u> in conjoined twins" and least complete in separate twins. Now, if greater degrees of reversal of asymmetry are expected when the epigenetic effect takes place early in relation to the twinning process, and if the greatest degrees are to be seen in conjoined twins, it appears that Newman still holds to his belief that conjoined twins represent twinning which occurs late in development whereas separate twins (the twinning process occurring so early that the epigenetic factors causing asymmetry reversal can do little more than produce minor changes) represent twinning which occurs early in development. However, it is difficult to know whether the criticism of Stockard may be considered an invalidation of Newman's theory for the production of SIVC.

E. Hereditary Considerations.

<u>1. General</u>

Such of the past theories, reviewed under History, above, as concern embryonic processes in relation to the origin of transposition, may here be considered hereditary except those already disposed of in the considerations just preceding. The vonBaer theory may be considered either hereditary or environmental (for the relation of the embryo to the yolk might be an inherited character; it might also be due to the physical influence of adnexae). Serres' theory (of the interdependence of the viscera like planets in the solar system) and all its corollaries, may be disposed of without deciding whether

they concern hereditary or environmental things, because (Lichtman, 158): "Pernkopf demonstrated that different organs or organ complexes or parts thereof may develop mirror-image position, and that the anlage of an organ in the sense of its normal or inverse symmetry exerts no influence on the development of the form or position of an adjacent organ.. ...A situs solitus of a single organ has been observed in spite of a general situs inversus. Cases of complete situs inversus with sinistrocardia must be considered instances. ...." It remains only to discuss the question of heredity in SIVC.

If SIVC could be shown to occur with significantly greater frequency among individuals who are blood relatives than in the general population, it would be safe to conclude that SIVC is an hereditary trait. Inasmuch, however, as the frequency with which this trait occurs in the general population is unknown, one would have to substitute for the general population a random sample of unrelated individuals who could be properly examined to determine whether they were affected with this transposed condition of the viscera. This work has not been done. Instead, there are a number of reports in the literature of the occurrence of SIVC in several members of a family, and the inference is drawn that this occurrence is an indication that SIVC is an inherited trait. The correctness of this inference could be established if sufficient pedigree data were available to enable one to establish a theory of the mode of inheritance and to test that theory in a sufficiently large group of families.

In a previous section a complete review of the recorded cases of SIVC, occurring in families, was given, and the work of Cockayne, in attempting to establish a mode of inheritance, was reviewed. The present author indicated that heresay evidence for the situs of the viscera in relatives of the affected person has been too much honored. In the present paper, a series of cases will be presented in which the most reliable (x-ray proof) evidence was relied upon.

Another method of approach to this hereditary study would be the investigation of twins, one or more of whom, in a given twin pair, were affected with SIVC. From the hereditary standpoint, the occurrence of any trait in twins is always worthy of investigation. If found in both members of a monozygotic twin pair and never found in one when not present in the other, a trait may be presumed to be hereditary because monozygotic twins have identical genetic constitutions. If found in one only of identical twins, the trait is assumed to be due to non-genetic factors which may affect the two members of the twin pair independently and differently. Consequently, the report of SIVC in twins proven to be identical would be a very important contribution to the question of the roll of genetic factors and etiology of this condition. In the following section all the reported cases of twins with one or both members of the pair having SIVC will be reviewed:

In case two, below, the difficulty of carrying on a genetic investigation among patients living in a large city is illustrated. None of the proband's ascendants could be contacted, and the study had to be confined to her descendants. Likewise, the case illustrating the Kartagener syndrone proved unsatisfactory because the proband's family all lived in a distant city. For this reason, the first series of cases, all from Montreal, are of less value as individual cases than as a group of families, which (if the group were thirty times larger) would be suitable for statistical analysis. However, in addition to these cases there are presented several coming from an entirely different type of community.

The last few cases are from rural North Carolina. It is a section of the country which was settled six to eight generations ago by people who have remained within a hundred or two hundred miles of the place in which their ancestors settled. As a consequence, there is high degree of inbreeding and, at the same time, it is possible to trace back all the relatives of any ordinary individual for a number of generations. This population is, therefore, almost ideal for hereditary studies. Unfortunately, SIVC is a condition which is not easily diagnosed by the physician unless he is on the look-out for it, and it is almost never diagnosed by the layman. Therefore, one cannot expect to obtain a reliable family history of this condition. On the other hand, inasmuch as the population of this section of the country marry young and usually have large families, it is possible to examine, within the course of a few weeks, fifty to seventy related individuals of two and three generations and, in this way, to obtain reliable pedigree data.

The question of whether SIVC is an inherited condition will be solved when two or three hundred cases have been assembled with proper objective study of all members of the family (sibs and parents of the proband), when evidence from twin cases with reliable diagnosis of zygosity is assembled, and when proper studies of large pedigrees have been made.

2. Twin cases of SIVC

> # "A.Z. ist als einzelnes Kind geboren worden. Ich erwähne das, weil die von H. Meckel (Müller Archiv 1850. S. 451) aufgeworfene und von mir (in diesem Archiv 1855. S. 522) näher erörterte Frage, ob unter freien Zwillingen bei dem einen eine Inversio viscerum workomme, wichtig, aber bis jetzt ohne thatsächliche Beanwortung gebleiben ist. Unter den von mir bisher beobachteten, auch unter den einem Ei entsprossenen Zwillingen, bestand bei keinem Heterotaxie."

This quotation from Schultze, 1861, is the earliest discussion of SIVC in separate twins that the present author has found. It dates from the same year as Forster's hyopthesis that SIVC always occurs in double monsters; and in this quotation of Schultze is mention of a paper by Meckel in 1850, not read by the present author, which may prove Meckel, not Forster, to have originated that hypothesis. Baron's report of SIVC in twins antedated this Schultze by many years.

Translation: A.Z. was a single-born child. I mention that because of the proposition put forward by Meckel and more recently by myself, whether visceral inversion occurs in one of separate twins; truly this, up to now, remains without factual verification or denial. In my previous experience with uniovular twins there was no heterotaxy.

"If a condition is inherited either as a dominant or a recessive it should affect both members of a pair of monozygotic twins, or neither." With that idea in mind from Cockayne, 1938, the Table IV dealing with cases in twins (cf. page 87) may be considered.

In 1912, Reinhardt reported twin brothers, age 20, with SIVC proved by x-ray. Kean (137a) quotes Reinhardt's proof of the diagnosis of zygosity as follows: "The external resemblance of the two is extraordinary. If one does not see them together and so observes that one is somewhat larger than the other, one continually confuses them; even neighbors and friends cannot distinguish between them." This evidence does not measure up to the scientific criteria of Norma Ford. The account of clinical evidence of cardiac pathology in one only of Reinhardt's twins throws some further doubt upon a diagnosis of monozygosity.

Norma Ford gives the following items* as proposed minimum requirements for a diagnosis of zygosity:

1. comparisons of physical characters such as hair color, skin color, hair form, etc.
2. comparisons of digital and palmar dermatoglyphic patterns.
3. detailed comparison of iris color and pattern.
4. blood group.
5. P. T. C. tests for taste.
6. record of the placenta (provided the information is reliable).
7. sole and toe dermatoglyphic prints.
8. comparison of the form and arrangement of the teeth.

Accepting these criteria of Norma Ford whose work is in agreement with that of the leaders in the field of twin diagnosis, we cannot properly consider Reinhardt's case one of proven monozygosity. In the same way, the remaining cases, given in table IV, will be considered.

*Items six to eight are desirable but not essential.

Pezzi and Carugati, in 1924, gave no diagnosis of zygosity.

Boccia and Maglione, in 1927, offered no proof of zygosity in their case.

Cockayne was unable to ascertain the zygosity of his 1938 case because one of the twins had died. The latest report, that of Kean, in 1942, concerning 18 year old girls, offers proof of zygosity which may be analyzed as follows:

1. comparison of physical characters
   a) hair of same shade, texture, amount, and curls
   b) skin of similar color and texture
   c) eyelashes and eyebrows similar
   d) lips and ears of same shape
   e) necks of same type
   f) hands very similar; slight difference in the fingernails
2. finger prints of the deceased girl not obtained
3. eyes of both were blue
4. blood groups not mentioned
5. P. T. C. taste testing not mentioned
6. "two placentas were present"
7. no sole and toe prints
8. teeth identical in size and texture, erupting at the same time.

The evidence in support of his diagnosis is insufficient, being solely qualitative in character, incomplete as judged by Ford's standards, and including no data from the two sibs and the parents.

Consequently, there is no completely acceptable <u>proven</u> case of SIVC in both of identical separate twins.

Discordance of Situs in Monozygotic Twins

In reporting his case of monozygotic twins in 1940, only one of whom had transposition of the viscera, Cockayne stated that there were four similar reports in the literature, and proceeded to review these. The present author has likewise reviewed these cases, and, on the basis of the data presented by the various writers in their attempts to establish the zygosity of the twins

TABLE IV

Cases in Twins

AUTHOR	DATE	SEX	NUMBER AFFECTED	MONO-ZYGOSITY
Baron (309)	1825	m m	1	questionable
Betschler-Tamm #(414)	1887	f f	1 (partial)	dissimilar
Hadden (352)	1890	f f	1	questionable
Miller (388)	1893	N.R.	1	questionable
Doolittle (333)	1907	m f	2 (partial?)	dissimilar
Reinhardt (408)	1912	m m	2	identical
Pezzi and Carugati (401)	1924	m m	2	questionable
Boccia and Maglione (315)	1927	m m	2	questionable
Dubreuil-Chambardel (75)	1927	m m	1	questionable
Araki (305)	1935	m m	1	questionable
Cockayne (52)	1938	m m	2	questionable
Cockayne (53)	1940	f f	1	identical

Reported by Friedrich Schatz (414)

he has discarded every case but that of Cockayne. A review of these cases follows, with reasons for their rejections as proven cases of SIVC in monozygotic twins.

a. Baron

Of this case, Cockayne writes: "Kuchenmeister states that the twins were monozygotic and that one had normal viscera and the other complete transposition." Here is Kuchenmeister's report verbatim:

> "N.B. Das Geschlecht des Kindes mit Situr transversus ist nicht speciell angegeben, geht aber hervor aus den Worten: 'Le frere jumeau de celui-ci, mort quelques jours apres, n'a offert aucune deviation dans son organisation'."

This may be translated: "The sex of the child with transposition is not designated, but is inferred from the words: 'The twin brother of this one, death some days later, showed no abnormalities in his situs'." There is nothing in this statement of Kuchenmeister and nothing in the original article, also consulted by the present author, to justify a diagnosis of monozygosity for these Baron twins. Therefore they must be discarded.

b. Betschler-Tamm

As related by Friedrich Schatz, these twins were born at 7 months and were female. There were no tests for identity. One was edematous and abnormal# in many ways, with partial situs inversus; whereas the other was normal apparently in every way (hence they were probably not identical). Cockayne correctly dismisses these from consideration as being twins in a case of <u>partial</u> transposition, therefore out of place in this discussion.

Herz und Aorta auf der rechten Seite gelegen; rechte Lunge fehlend, linke klein; Zwerchfell normal; Leber abnorm und lappig; Nieren sehr gross und etwas mit Wasser durchtränkt; Trachea und Oesophagus verschlossen."

c. Hadden

This is a case not mentioned by Cockayne. The reporter states that the proband was R-handed and had a L-handed sister with normal situs who bore remarkable resemblance to the patient. The twin (unaffected) sister was made to use her R hand in school but still preferred the L for many household duties. The girls had a brother, one of twins, who was said to be L-handed, but I could not obtain an opportunity of examining him". Here was a wealth of potentially invaluable material - forever lost to medical science. There is no proof of zygosity. The case must be discarded.

d. Miller

Cockayne's comment sufficiently characterizes the article by this reporter: "Miller (1893) records a case of monozygotic twins, one with situs inversus viscerum and the other with situs solitus, but gives neither their age nor sex". He likewise gives no absolute proof of monozygosity. Consequently the present writer will not accept this as a proven case of SIVC in only one of monozygotic twins.

e. Dubreuil-Chambardel

No proof of monozygosity is given. They are aged 25 and referred to in the masculine gender and they both have varicose veins on their legs, appearing about the same time in about the same place. The one has harelip on the R and his twin on the L, but the author neglects to state which-sided harelip accompanies the visceral transposition (which was proven by x-ray). Because

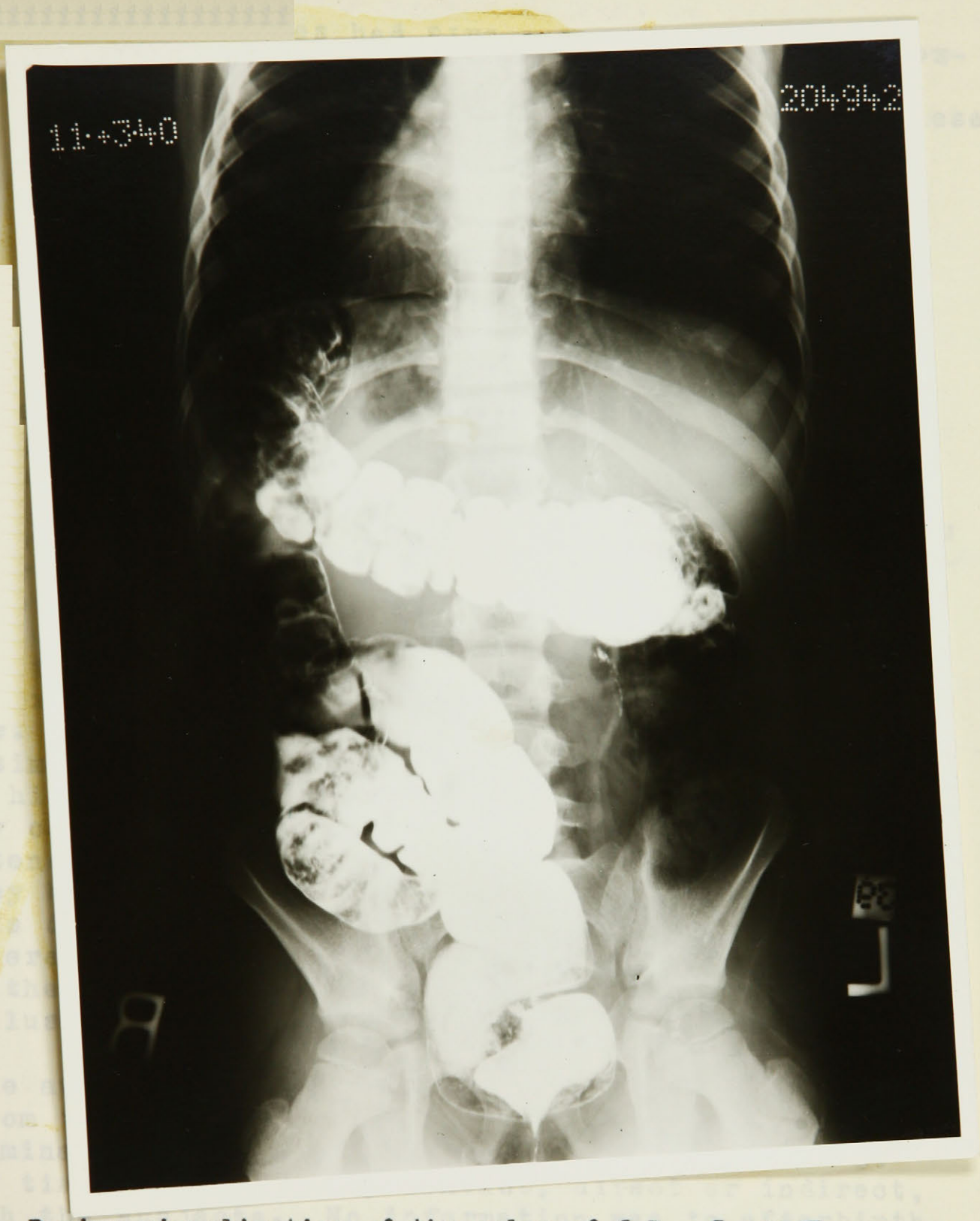
proof of identity is not presented this case also cannot be accepted.

Cockayne, in reviewing this case has unfortunately confused the record of these twins with another pair of twins reported in the same article, when he writes: "Dubreuil-Chambardel (1927) records male twins, aged 25, identical in general appearance, in weight, height, and in physical characters. Each had varices on the lower limbs of the same type and developing in the same way. One had harelip on the left...etc." Actually what is given in the preceding paragraph is all that the original paper gives about the twins with transposition. The matter regarding the general resemblance in weight, height, voice, disposition, and growth, concerns the second set of twins, both of whom had normal situs (possibly, for no record is given of this), and both of whom had harelip - one on the R and one on the L.

f. Araki

This case was reported in Cockayne's paper (1938) as an instance of SIVC in both of monozygotic twins. He later recognized, however, that only one of these boys was affected. Cockayne explains that he has not seen the original article, "but Taku Komai, though he gives neither their age nor sex, says they were monozygotic and that one had normal viscera and the other complete transposition". The present author obtained the original at the New York Academy of Medicine. The German abstract to the Japanese article states that the boys (aged 25) were monozygotic twins, showing no congenital defects on general clinical examination. But EKG and x-ray revealed that twin A had

Illustration XII



Barium visualization of the colon of J.R. Case IV

Transposition of the colon is demonstrated. The barium clearly demarcates the transverse colon rising from hepatic flexure on the L to splenic flexure on the R. The descending colon is on the R, ending in the sigmoid, which, contrary to the findings in situs solitus, occupies the R posterior quadrant of the pelvis. (Courtesy Dr. J.G. Munroe and Department of Radiology, Royal Victoria Hospital, Montreal).

transposition while twin B was normal. There were no other children by the mother of the twins, but there were normal twins (without inversus) by their father's second wife. No near relatives had SIVC. In the abstract no explanation is given of the means employed to determine these things. A is L-handed and B is R-handed.

A translation of the Japanese text provided by an oriental scholar in New York is summarized in his own words as follows:

> "The twins, whose family name was Y. were 34 years old, both male. They were born in Ehime Prefecture, Japan, so alike in facial characteristics, physique and general bearing that even their closest relatives sometimes had difficulty in telling them apart. Neither had in the past been taken seriously ill, and were quite healthy.
>
> "In the spring of their 28th year, twin A. noticed an extra tooth beginning to grow in his right upper jaw. A few months later, the other twin B. noticed a similar occurrence at an almost identical location in his right upper jaw. As in neither case was there any conscious irritation, this condition was left unattended for several years, until in their 34th year they both simultaneously consulted a dentist, K. This dentist K. considered their case as being of much interest, and after extraction, made a plaster cast of the jaws and sent this material to the author. (Illustrations 1. and 2.)
>
> "The author then subjected these casts to examination. (From the article, no other material was used in this examination. The author does not indicate that at any time had he had any contact, direct or indirect, with the subjects. No information was to afterbirth, finger prints, or blood groups, etc. No genetic study made.)
>
> "The number of extra teeth in both twins was limited to one each, their shape both being coniform. The one extracted from A. was slightly wider than that from B. whose tooth was slightly sharper in appearance.
>
> "With the above evidence, the author seems satisfied to treat this example as a case of uniovular twins, and goes on to describe a psychological affinity.

"Very soon after the teeth were extracted, A. felt the desire to immigrate to Brazil, and made the necessary applications. Whereupon, B. felt that he could not stay alone in Japan without A. and so decided to make similar applications and share whatever life might lie ahead. Thus both A. and B. went to Brazil together, but on arrival, after a few months, both took ill, and both died within a few days of each other. (The author does not state any further information concerning their illness in Brazil beyond what is given above.)

"From these above points, the author concludes that not only similar physical characteristics, but even a similar fate had been "naturally given" to these twins at the time they had been conceived and the ovum split, a 'phenomenon seen only in the case of uniovular twins'. (!!!)

"In his conclusion, the author gives a summary of the above, and submits the article as an example of uniovular twins.

"To the ordinary layman such as myself, this case seems not above question. The author does not substantiate the existence of the twins. He has had no personal contact with them, the material he uses is limited to two plaster casts of their upper jaws. He says nothing of the early history of the twins, and within a few months after the author's knowledge of their existence, the subjects leave for a foreign country, and die!"

There are several indications in this paper that the twins may be monozygotic but no actual proof. A question of great interest is brought forward by this report. If the boys were indeed monozygotic and only one had SIVC, the appearance of the extra tooth on the R side of both A and B may be an example of a part of the body (the teeth) not affected by transposition in SIVC. On the other hand, it may be that identical twins with the ordinary degree of mirror imaging would have such an extra tooth one on the R and one on the L, and that therefore the appearance on the same side in the two boys represents a transposition of situs in one. (This matter should be considered in conjunction with Jasper-Raney studies of EEG, as reported above

where mirror imaging of the EEG is the normal condition in some normal identical twins.)

In requesting the translation of Araki's article, the author provided the translator with a list of specific questions regarding the establishment of the study, and heterotaxy aspects. Consequently, in the light of his report it seems reasonable to conclude that Araki's twins may not be considered as a proven example of SIVC in one only of (unquestionably) monozygotic twins.

g. Cockayne

The writer has sent to Cockayne for certain items of further information to make doubly sure that his case is actually one of monozygotic twins. The absence of other proven cases makes this one in almost undoubtedly, monozygotic, thirteen year old English girls, extraordinarily important, and a wrong interpretation must not be permitted. Analyzing his material in terms of the criteria of Norma Ford, we have the following:

1. comparisons of physical characters
   a) similarity of hair color and hair whorl
   b) quantitative measurements:

	EILEEN	JOAN	DIFFERENCE
Stature	1429	1437	- 8
Left cubit	396	396	0
Right cubit	397	396	+ 1
Maximum head length	180	184	- 4
Maximum head breadth	136	136	0
Head height	128	125	+ 3
Cephalic index	75.6	73.9	
Bizygomatic breadth	121	121	0

These measurements appear to have been very carefully done. It would have been an improvement if something of the method (number of independent measurements, instruments used, etc.) were known.

2. comparisons of digital and palmar dermatoglyphics

John W. McArthur ( ) has stressed the importance and the necessity of studying other sibs and the parents in attempting zygosity diagnosis. Cockayne gives ridge counts for the twins only.

3. iris color and the pattern

Cockayne remarked on the similarity of the iris pigmentation and other eye characteristics (pupillary membrane, etc.)

4. blood group

The present author pointed out (312) previously that there are many pitfalls in blood grouping. Without knowing more about the technique used by the collaborator who typed the blood of Cockayne's twins it is impossible to appraise the reliability of the hemagglutination report. Group O is the largest blood group; but it is not difficult to misdiagnose group A_2 as O. This is true because the agglutinin for A_2 is not found in all B blood in strong enough titer to be employable as a typing serum, the agglutinin of A_1 is present in strong titer. Consequently, such serum will be useful for agglutinating corpuscles with A_1 agglutinogen, but not for corpuscles with A_2 - and yet this fact goes unrecognized in many laboratories. A_2 blood, typed with such sera will fail to show agglutination and will therefore be categorized as O blood. To obviate this possibility, one should test anti-A serum with known A_2 corpuscles or use known A_2 blood as a control in experiments when anti-A serum of unknown character is employed.

5. PTC

PTC testing, unless done with crystalline PTC, may lead to false conclusions. The writer has had experience with PTC impregnated paper tested in paralled with PTC.

crystals and he found the latter detected the ability to taste this substance when the paper failed.....very often. There is no explanation of the method used by Cockayne.

Altogether, the case which Dr. Cockayne presents is the best one in the literature of SIVC in twins. Were the situation he presents (which seems to be so very important theoretically) a well established entity, there would be no hesitancy in accepting his diagnosis of monozygosity on the basis of his material, just as presented. However, until other cases are reported, at least one, in sufficiently great detail to establish incontrovertible evidence that the entity of SIVC in one only of monozygotic twins, does exist, it is necessary to be somewhat reserved in judgment of Cockayne's twin girls.

3. Conclusion from twin cases

The present author has no reasonable basis for believing that SIVC has been observed in both of monozygotic twins. In the author's correspondence with Dr. Cockayne, the latter has written that he has lost touch with the twins, owing to the war, and that he has little hope of applying additional tests. The tremendous theoretical importance of Dr. Cockayne's case makes it seem reasonable to reserve judgment until a second similar case, more completely and convincingly studied, has been reported. Meanwhile, reasonable doubt exists ~~that these sisters are in reality identical twins~~.

pressive, especially for girls whose environment is identical.

The quantitative measurements, however, appear to be very carefully done. Here too it would be an improvement if something of the method (number of independent measurements, instruments used, etc.) were known. Cockayne's table is herewith reproduced:

	EILEEN	JOAN	DIFFERENCE
Stature	1429	1437	- 8
Left Cubit	396	396	0
Right Cubit	397	397	1
Maximum Head Length	180	184	- 4
Maximum Head Breadth	136	136	0
Head Height	128	125	3
Cephalic Index	75.6	73.9	
Bizygomatic Breadth	121	121	0

Eileen is the girl with the SIVC.

Altogether the case which Dr. Cockayne presents is the best one in the literature from the standpoint of zygosity diagnosis. Were the situation he presents (which seems to be so very important theoretically) a well established entity, there would be no hesitancy in accepting his diagnosis of monozygosity on the basis of his material just as presented. However, until other cases are reported, at least one in sufficiently great detail to establish incontrovertible evidence that the entity of SIVC in only one of identical twins, does exist, it is necessary to be somewhat reserved in judgement of Cockayne's twin girls.

3. Conclusion from twins cases.

Until an opportunity to read Reinhardt's original article occurs, the author has no reasonable basis for believing that SIVC has been observed in both of monozygotic twins. Until further is obtainable on the girl twins of Cockayne, slight doubt will remain in the author's mind

that these sisters are in reality identical twins. This doubt has not been lessened by the translation of Araki's article on his boy twins because the report has less acceptable proof of the identity of his brothers.

Cockayne ably explained alternative possible mechanisms for the appearance of SIVC in only one of a pair of identical twins (52). These explanations he abandoned in 1940 (53). "If Newman's views about mirror-image formation are accepted, the very rare cases of human monozygotic twins with a mirror image arrangement of the viscera in addition to that of ectodermal structures are due to an unusually late fission." Here again is the environmental argument against which can be rallied only that criticism of Newman's views on twinning which Stockard made in 1920-1, given above (page 83).

The cytological explanations used by Crew and Munro for gynandromorphs could be applied to explain Codkayne's twins on genetical grounds. Non-disjunction, with one sib receiving two dominant alleles and one recessive of the autosome determining situs, while the twin sib (half of the zygote) received one recessive allele and nothing more, could explain the phenotypic manifestation of a recessive character in one only of identical twins. It would have, as an explanation, the advantage of overcoming the objection Cockayne advanced to his own explanations ("the improbability of so unusual an occurrence happening in at least five recorded cases"), since non-disjunction might prove to be a characteristic of the autosome deter-

mining situs (a characteristic only becoming manifest under this circumstance, i.e. twinning).

A similar case can be made for the elimination hypothesis. In upholding either explanation, it will be necessary to search for other characters present on the autosome in question, the linkage of which will be shown by the degree of presence phenotypically in the twins. Until, however, someone can demonstrate at least one character which is linked with the factor for situs, or until more careful examination of Cockayne's girls is made, with this idea of linked characters in mind, these explanations of the conditions cannot be upheld or entirely rebuked.

4. Conclusions on hereditary considerations

The writer believes that insufficient data have been accumulated for any proper conclusions to be made on this question of the role of hereditary factors in the etiology of SIVC. Even the addition of the handful of cases reported below, provides no certain clue. The previous work is not sufficiently objective or thorough to be utilizable in a scientific appraisal. Conclusions in regard to this question lie entirely with the future. Cockayne's work reported above is the best knowledge available to date, and his theory of a single Mendelian recessive autosomal factor as the cause of SIVC can be upheld even in the face of the occurrence of SIVC in one only of monozygotic twins, if incontrovertible proof of such occurrence be advanced.

F. Conclusions on etiology.

The method of production of SIVC is certainly not known. A review of the theories and hypotheses advanced by ovservers since vonBaer (1828) shows that explanations postulating deviations from normal developmental processes have been most popular. The modern and well substantiated variant of this explanation is the developmental arrest theory of Stockard et al. This may be safely applied to the case of SIVC without committing the applicant to any stand:

1. as a unitarian - one and only one mode of production.
2. as an environmentalist (Newman) environment causing developmental arrest
3. as a dualist (Cockayne):
    a. single Mendelian autosomal recessive for SIVC in single individuals
    b. environmental theory of Newman for SIVC in monozygotic twins

It is not outside of reason to suppose that SIVC may be caused by developmental arrest which may be due to hereditary factors in the embryo, to disease (infectious or otherwise) in the maternal tissues, and also due to a specific gene for visceral transposition. The occurrence of all types of malformation including situs transpositus in Stockard's fish certainly cupports his contention that ANYTHING can happen following developmental arrest. There are, on this basis, numerous points at which hereditary factors could be operative in producing transposition:

1. on maternal organism, causing poor oxygenation by faulty placentation or otherwise
2. on embryo causing development so rapid that placentation occurs while still in tube where oxygen supply will be inadequate, causing arrest
3. on embryo causing development so slow that implantation occurs at the cervix where the placenta will

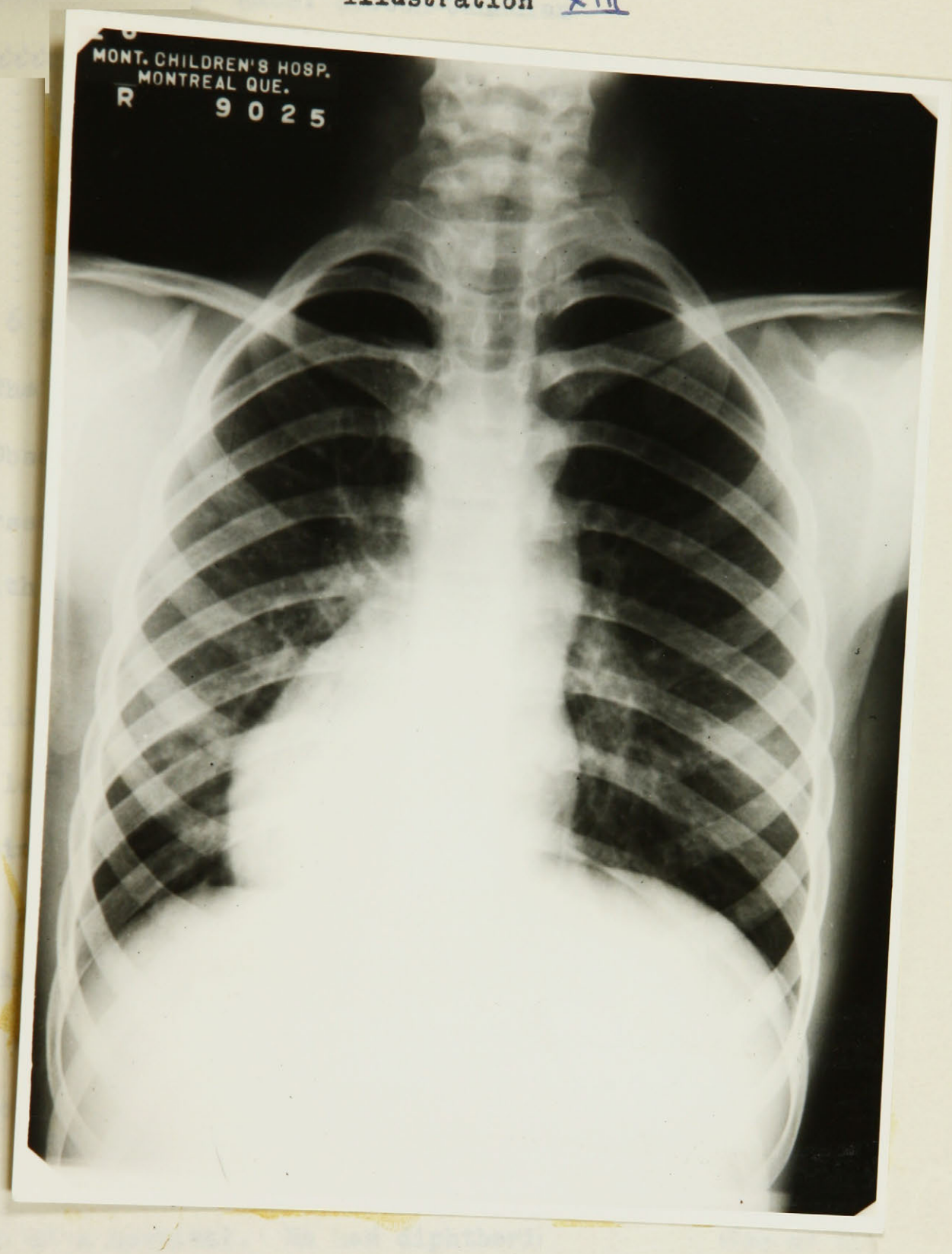
be so poorly situated that faulty oxygenation will result, causing developmental arrest

4. on embryo, after developmental arrest from any cause has occurred, making SIVC, rather than some other malformation, the resulting structural deviation
5. and innumerable others

VI. PRESENTATION OF CASES

The first group of cases presented below is from Montreal. Case I was encountered by chance. Every bit of information about this person and his family was obtained through the personal efforts of the author. Proper acknowledgments of the assistance received by the author in the study of this case and the other cases is given at the end of this section under the heading, Acknowledgments. After having seen the first case, the author went through the records of all the teaching hospitals at McGill, hunting for additional cases, which were found listed not under the heading of situs inversus viscerum but under various other headings such as congenital heart disease. In addition, the author went personally to various clinicians in Montreal and asked them for their cooperation in locating new cases. One doctor, who had encountered such a case in his practice, permitted the author to study his patient. Every case report is to be considered the original work of the author.

Illustration XIII



Chest plate of G.P. Case VI

Dextrocardia is demonstrated. (Courtesy of Montreal Children's Hospital).

VI. PRESENTATION OF CASES

Case I

1. Age: 27 Sex: male Race: Scotch-Canadian

2. Complaint: pneumonia at 26 years.

3. Personal History:

The proband was born in Montreal, of a 32 year old mother on May 15, 1914, the second of boy twins, weighing 6 pounds. Delivery was at home, an easy and rapid labor. The child was strong at birth, no abnormalities were noted. Observations on the placenta are not remembered. The twins nursed at the breast for almost two years, enjoying fine health without cyanosis, convulsions, fever, or allergic diseases. The first teeth appeared at 6 months, walking began at 10 months, talking at 2 years. He entered school at 7 years, losing no time from illness or backwardness in studies, and skipping no grades during his 7 years attendance. L.H. was adept at swimming, basketball and hockey. Following school-leaving, he entered a night school for a course in accounting, then took a technical course in running business machines. Finally he began as a stenographer, became a business machines operator, and finally a technician in the electroencephalography department of a hospital. He had diphtheria at 3, measles at 6, pertussis at 8, pneumonia at 20 and 26. L.H. is unmarried and lives at home with his parents, his twin brother, and several sisters. He denies any intratheracic diseases other than those mentioned, and is not troubled by sinusitis.

4. Evidence for diagnosis of SIVC:

   a. physical examination: by the methods outlined above (page 14), L.H. shows typical SIVC and no associated congenital anomalies.

   b. x-ray of the chest: dextrocardia: barium meal x-ray: SIVC.

c. EKG of the heart with usual and reversed leads: dextrocardia.

5. Surgical procedures: no operations.

6. Complications:

The occurrence of pneumonia in one only of twins whose personal history is otherwise practically identical, and whose environment has been the same#, arouses a suspicion that the "pneumonia" may not have been pneumonia, but possibly early bronchiectasis. A lipiodol study will be done as soon as the patient's cooperation is obtained. Both testicles are well descended, the R. lower than the L; The hernial rings are not enlarged; there is no sign of CHD.

7. Handedness:

L.H. was formerly L-handed and was forced to change in school (4th grade). He is still ambidextrous in hockey, but R-handed in all other play, in writing and in work. The result of the EEG on L.H. has already been given (cf. Illustration no. X, following page 56).

8. Etiology:

a. Family History: all members were examined in accordance with a method of study described elsewhere (311), the results of which are summarized in Table V. A pedigree chart of this family is herewith presented, indicating that twins occurred in the same and succeeding generations: maternal male cousins, and in a miscarriage (at 5 months) of a sister. No malformations have been recorded in the family. A special investigation was undertaken to determine whether the proband and his twin were fraternal or identical in view of the findings of Newman (393) that twins with extensive mirror-imaging are less similar than completely identical (non-mirror-imaging) twins.

vonVerschuer is quoted by J.A.F. Roberts (411) as stating that the number of affected identical twin sibs of persons with pneumonia is only slightly more than the number of affected fraternal twin sibs, showing that heredity is of little importance in this disease.

TABLE V

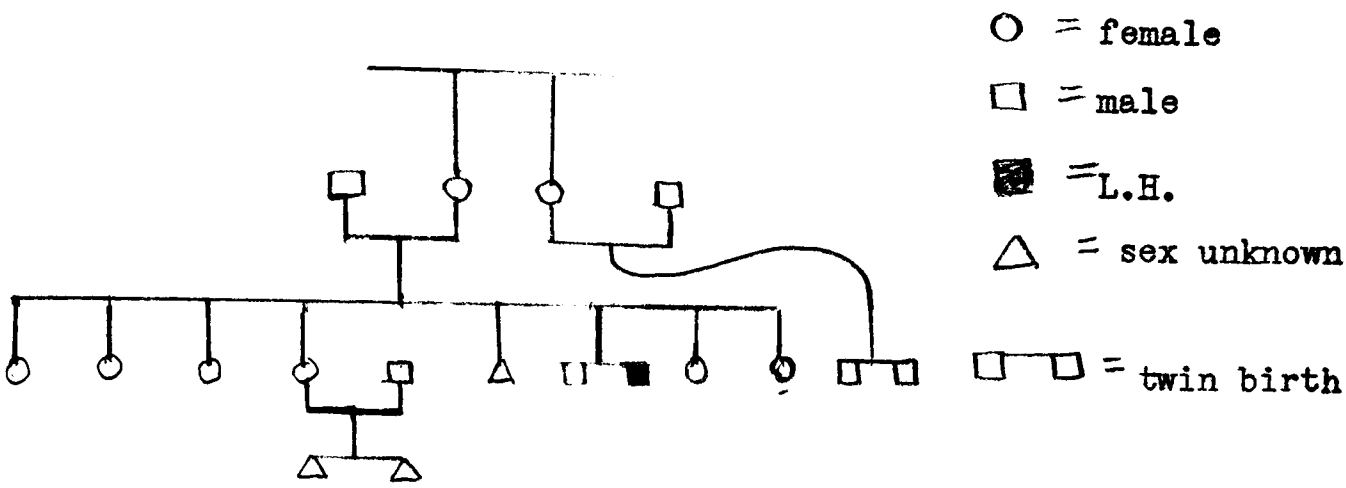
C.R.	SEX	BIRTH	SIVC	BLOOD	WHORL	HAIR COLOR	EYE COLOR	PTC	MANNOSE
1	F	5/7/05	no	?	c	bl.	blue	yes	?
2	F	6/4/07	no	AB MN	c	bl.	blue	yes	no
3	F	5/20/09	no	B MN	cc	bl.	blue	yes	minty
4	F	8/14/11	no	O ?	c	bl.	blue	no	no
5	?	aborted 4-5 months; possibly twin embryo							
6	M	5/14/14	no						
	M	5/15/14	yes		other details elsewhere				
7	F	8/17/16	no	B MN	cc	bl.	blue	yes	sweet
8	F	4/27/19	no	AB MN	c	br.	blue	no	no
Father		8/1/81	no*	A MN	?	?	?	(no)	chalk
Mother		1/8/83	no	B M	?	?	?	(no)	minty

*by physical examination

ABBREVIATIONS

C.R.	conception rank
F, M	female or male
SIVC	evidence of presence or absence, by x-ray
Blood	results of hemagglutination tests
Whorl	C if clockwise, cc if counter-clockwise
Hair color	bl. for blond br. for light brown
Eye color	blue; br. for brown
PTC	phenylthiocarbamide: yes if tested with crystals; no if not tested with crystals; (no) tested with paper

The proof of non-identity is summarized in Table VI. A complete dermatoglyphic study of this family (analyzed for the author by J.W. MacArthur of Toronto) also shows the twins to be dizygotic.



b. Syphilis: no serological evidence is available or obtainable for the parents or affected sib. History, physical examination, and general character of the home argue against syphilis in this family.

c. Alcoholism: history negative.

d. Maternal disease in pregnancy: the mother noted nothing unusual about this pregnancy and declares that she was well throughout.

e. Geography: the parents have lived in Montreal steadily since marriage.

9. Hospital admissions:

No pertinent data are contributed by the known, available hospital admissions.

10. Conclusion:

Case I is a proven case of SIVC, occurring in one of very similar but dyzogotic twins. It cannot be contended that the boys are ordinarily mistaken for one another. The similarity in their appearance is not sufficient for that. P.H. started life as the heavier, weighing 6 3/4 pounds at birth and 16 3/4 pounds at six months. As shown by Table VI, he is still the bigger in most measurements. L.H. weighed 6 pounds at birth and 16 3/4 pounds at six months, but today he is smaller than his brother in most measurements. Observations on the placentae are not available as in the case of the Kean twins. The Kean

TABLE VI

Skin color	pale (indoor work) fair	slightly ruddy (outdoor) fair
Hair color	sandy blond	sandy blond
Eyes	blue (green tint)	ditto
PTC taste	bitter	no taste
Mannose	chalk	sweet and minty
Blood	A_1B MN Rh non-secretor	A_1B N Rh secretor
Standing height	5'8"	5'10"
Sitting height	35 5/8"	36 1/4"
Occipito-mental	22 1/2cm.	23 cm.
Biparietal	14 1/2cm.	14 cm.
Basi-alveolar	15 cm.	15 1/2cm.
Basi-nasal	14 1/2cm.	16 cm.
Bizygomatic	12 cm.	13 cm.
CLOTHING SIZES:		
socks	11 1/2	11
shoes	8 1/2	8
gloves	8	9
hat	6 3/8	6 7/8
suit (shoulder)	38	38
shirt neck	14	14 1/2
shirt sleeve	33	34
waist	30	32

twins, supposedly monozygotic, weighed six pounds and four pounds, and there were two placentae present. Anthropometric data on the Kean twins in adult life are not given in Kean's article.

The following are the chief values of this case report:

(1) A study in the inheritance of various apparently unrelated factors distributed in the parents and among the sibs of a person with proven SIVC.

(2) Positive establishments of a diagnosis of dizygosity in a pair of similar male twins, one only of whom is proven to have SIVC.

(3) Acceptable clinical evidence of the distribution of visceral situs throughout the sibs and parents of a person with SIVC.

Case II

1. Age: 37 Sex: female Race: Italian-Canadian

2. Complaint: acute rheumatic fever at 30 years.

3. Personal History:

The proband was born in Montreal, February 4, 1905. She was a healthy child, but had measles and in 1918, influenza. At the age of 30 the patient spent six weeks in the hospital, suffering from acute rheumatic fever. She denies any intratheracic disease other than that mentioned, and is not troubled by sinusitis. She was married June 7, 1920, in Montreal to a man 18 years older, unrelated, born in a part of Italy one day distant from the home of her forebears. The husband died of cardio-renal disease in January, 1942.

4. Evidence for diagnosis of SIVC:

   a. physical examination: by the methods outlined, M.Y. shows typical SIVC and no associated congenital anomalies.

   b. x-ray of the chest (Illustration no. I): dextrocardia; barium meal x-ray: SIVC (Illustration no. II).

   c. EKG of the heart with usual and reversed leads (Illustration no. VIII): dextrocardia.

   d. gall bladder visualization: sinistroposition of the gall bladder.

5. Surgical procedures: no operations.

6. Complications: none.

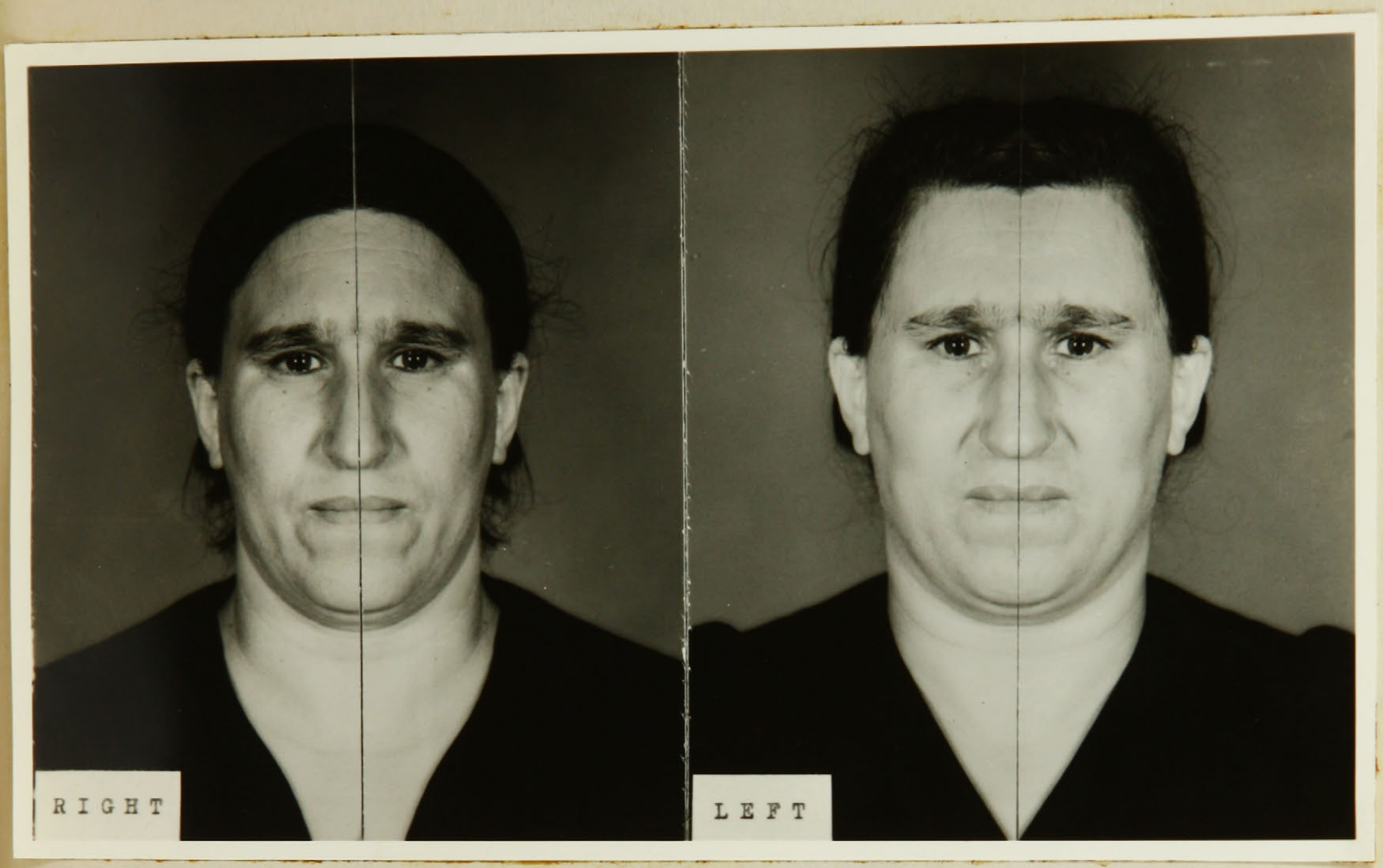
7. Handedness:

M.Y. has not learned to read or write. She performs all household and other tasks with her R hand and has never been aware of ability to use the L hand effectively. No tests were performed.

8. Etiology:

   a. Family History:

Illustration XIV



Split photograph of R-handed person with SIVC. Case II

The side shown to be the larger is the L, suggesting L-sided cerebral dominance. This in in harmony with the R-handedness. No EEG data available.

TABLE VII

C.R.	SEX	BIRTH	SIVC	BLOOD	WHORL	HAIR COLOR	EYE COLOR	PTC	HOSPITAL ADMISSIONS
1	M	born dead							
2	M	died meningitis at 5 months							
3	M	10/17/23	no	A MN	C	D.br.	br.	yes	4
4	?	miscarriage at 2 months							
5	M	10/22/25	no	A MN	C	br.	blue	yes	none
6	M	5/20/27	no		C	D.br.	br.	yes	1
7	?	miscarriage at 7 months							
8	M	11/7/29	no	A MN	C	D.br.	br.	yes	none
9	M	6/24/31	no	A MN	C	D.br.	br.	yes	1
10	F	3/4/33	no	A MN	C	br.	br.	yes	none
Mother		2/3/05	yes	O MN	C	D.br.	br.	no	2
Father		5/9/87	(no)	?	?	(black)	(blue)	?	6

ABBREVIATIONS

(as given following Table V, with the addition of the following:)

D.br.	dark brown hair
M.T.	indicates name of proband
(no), (black), (blue)	information about the dead father obtained from conversation with his widow.

1) ascendant: M.Y. was the first living child of her father's first wife (two previous children of unknown sex died shortly after birth of causes not known to the proband). A younger sister and brother, not contacted by the author, are alive and well, in Montreal. The disposition of the viscera in the deceased mother, the surviving father, and the two living sibs (and thw two dead sibs) is not known. Work is under way to investigate the matter in the surviving relatives. No knowledge of multiple births or malformations was elicited.
2) descendant: M.Y. has been pregnant ten times. Table VII gives a record of the genetic investigation carried out on her family. All the living children were personally examined. X-ray methods were employed, as in Case I, to determine unequivocally the situs of the viscera.

b. Syphilis: the proband's Wassermann was negative at the time of her admission at 30. There are no signs of syphilis. Knowledge of syphilis in her antecedents is not available. Her husband's serology was negative.

c. Alcoholism: no history of this was obtained.

d. Maternal disease in pregnancy: history of this not obtainable bacause the proband's mother is dead.

e. Geography: the proband's family lived in Montreal.

9. Hospital admissions:

Other than their service in verifying anamnestic data, the two admissions of the proband are of no help. Unfortunately there are no hospital records of her deliveries because her children were all born at home.

10. Conclusion:

M.T. is a proven case of SIVC. In case I complete data on the ascendants and sibs of the proband was given. In this case, data of the ascendants is unavailable, but a complete study of various independents, hereditary traits in the descendants is provided. A conclusion regarding etiology cannot be drawn from this single case on the basis of the information available.

Case III

1. Age: 10 months Sex: male Race: French-Canadian

2. Complaints: marasmus at 10 weeks.

3. Personal History:

The proband was born in Montreal, May 18, 1941, the twelfth pregnancy of his 31 year old mother; the delivery was at home, by a physician. The baby was apparently two weeks premature, weighing $6\frac{1}{4}$ pounds. It was noted at birth that neither testicle was descended. Because of breast abcess development in the mother, the child was suckled only two weeks and then artifically fed. At two months the child weighed only 5 pounds 9 ounces, and was admitted for complaints of vomiting and feebleness. X-rays were taken for the confirmation of spina bifida occulta because of a patch of hair over the sacral spine; this was not confirmed. The record of the physical examination shows that both testicles were in the scretum at two months. The improvement obtained by hospitalization did not continue after discharge and the child was readmitted in August. At that time chest x-rays and barium series were done and the Wassermann was found negative. In October the child reentered the hospital with the diagnosis of otitis media and marasmus, whereupon the previous findings of visceral transposition were confirmed. The author examined the child in January, 1942, and learned that its condition since the October admission had been improved.

4. Evidence for diagnosis of SIVC:

   a. physical examination: the heart was found dextroposed, the stomach and liver transposed, the R testin lower than the L.

TABLE VIII

C.R.	SEX	BIRTH	SIVC	BLOOD	WHORL	HAIR COLOR	EYE COLOR	PTC	HOSPITAL ADMISSIONS
1	M	10/10/29	no	A M	C	br.	blue	no	2 plus OPD
2	M	1/7/30	no	A M	C	br.	blue	yes	1 plus OPD
3	F	8/16/32	no (post mortem) died 4/28/33						1 mastoiditis
4	F	6/13/33	no	A Mn	C	D.br.	D.br.	yes	4 plus OPD
5	?	miscarriage at 2 months							
6	F	10/?/34	no	A M	C	br.	br.	yes	none
7	M	3/27/36	no	A MN	C	br.	br.	yes	none; OPD
8	M	9/?/37	no	A MN	C	br.	blue	yes	none
9	?	miscarriage at 2 months							
10	M	8/?/39	died at home, at 3 months, unknown cause						
11	M	4/?/40	no	A MN	C	br.	br.	yes	none
12	M	5/18/41	yes	A MN	C	?	?	?	3
Father		1900	?	?	?	?	?	?	?
Mother		1910	no	A MN	C	D.br.	D.br.	yes	1 or more

ABBREVIATIONS - cf. Tables V and VII.

b. x-ray of the chest and abdomen: dextrocardia and SIVC; barium examination of the gastro-intestinal tract (Illustration no. III): SIVC.

c. EKG is pathognomic for dextrocardia of SIVC.

5. Surgical procedures: none.

6. Complications:

The cryptorchidism present at birth bilaterally was corrected by normal descent of the testes during the first two months of life.

7. Handedness: no evidence.

8. Etiology:

a. Family History: Table VIII gives data from the genetic investigation of the family of J.A. There is no information as yet available about the father from observation because he has been out of town. There is no record of multiple births or malformations.

b. Syphilis: the serology of the mother and proband is negative for lues, both taken since the child's birth. The paternal Wassermann is not known.

c. Alcoholism: there is no history of alcoholism.

d. Maternal disease during pregnancy: the mother denies any disease during pregnancy.

e. Geographical environment: the parents have lived in Montreal since marriage.

9. Hospital Admission: Incorporated above.

10. Conclusion:

J.A. is an individual with SIVC which was discovered during the first year of life. As in the two preceding cases, the visceral transposition seemed to play no part in producing the physical or physiological maladjustment to environment which brought the patient to the physician. This is the third consecutive case in which there is no family history on the basis of anamnestic data or on the basis of objective data of transposition in other members of the family.

Case IV

1. Age: 10 Sex: female Race: Scotch-Canadian

2. Complaint: sinus trouble at 9

3. Personal History:

J.R. was born in Montreal at the R.V.M.M.H. on April 5, 1932, the product of her 22 year old mother's fourth pregnancy. The proband weighed 3400 gms., was full term (calculated date of delivery was three days earlier than the actual date), and was born by medically induced labor. The placenta was bilobed#, according to the hospital records. The child was breast fed, gained weight rapidly, and has been a normal, healthy child since. She had one admission to the contagious disease hospital (scarlet fever?) and no other cause for medical attention until the complaints of sinusitis in 1940. At that time x-rays of the skull were taken, but no serious sinus involvement was found. She has not had pneumonia, pertussis, measles, or other intratheracic disease.

4. Evidence for diagnosis of SIVC:

   a. physical examination: by the methods outlined, shows typical SIVC and no congenital anomalies associated therewith.

   b. x-ray: chest plate and barium visualization of the G-I tract demonstrate SIVC.

   c. EKG of the heart: usual and reversed lead demonstrate typical dextrocardia of SIVC.

5. Surgical Procedures: none.

6. Complications: as given on the previous sheet.

7. Handedness:

The mother reports that the proband is L-handed in everything and that no attempt has been made in school to alter this. J.R. made a record of her hand-writing with both R and L hands, and the L-handed writing is obviously clearer and more natural. None of the

other children (nine altogether) demonstrate L-handedness with the possible exception of the two-year-old twin. The sinus plates do not show clearly which side of J.R.'s skull is larger. Anthropometric measurements show the right arm 1/8 inch shorter than the left. The R bicep 3/8 inches larger than the L; the R forearm 1/4 inch larger girth than the L. Several of the skull measurements, larger on the L half than on the R. This only serves to cloud the picture, inasmuch as one expects the dominant hand and arm to be larger and the contralateral side of the skull to be larger than the homolateral side.

8. Etiology:

a. Family History: all members of the family except the father, who is a soldier overseas, has been personally examined. A dermatoglyphic study of the family has been completed, demonstrating that the twins are truly monozygotic. Records from all hospital admissions have been consulted. All members of the family, except the father, have been examined by x-ray and found, with the exception of the proband, to have situs solitus. Table IX embodies the result of the genetic studies on this family. There are male twin cousins in the family of the father. These cousins each had a pair of twins, one set like-set, male twins; one set unlike-set of twins. No malformations are known of in the family anywhere.

b. Syphilis: as on the previous sheet.

9. Hospital admissions:

The hospital admissions for the proband have already been summarized. Admissions of all other members of the family have been utilized in checking anamnestic data.

10. Conclusion:

The case of J.R. illustrates again the possible relationship between a family history of twinning and the occurrence of SIVC;from anamnestic data and from examination of the sibs and one parent there is no evidence of SIVC in anyone but the proband. The possible etiologic relationship of the bilobed placenta observed at the birth

TABLE IX

C.R.	SEX	BIRTH	SIVC	BLOOD	WHORL	HAIR COLOR	EYE COLOR	PTC	HOSPITAL ADMISSIONS
1	M	9/25/27	no	OMN	C	D.br.	hazel	no	1
2	M	10/1/28	no	OMN	C	Br.	blue	no	3
3	M	5/6/30	no	OMN	C	Br.	hazel	yes	none
4	F	4/5/32	yes	OMN		Br.	hazel	no	1
5	F	9/16/32	no	OMN	C & cc	Bl.	blue	no	2
6	M	7/3/35	no	OMN	C	Br.	hazel	no	1
7	M	1/2/37	no	OMN	?	Br.	hazel	no	1
8	F	1/27/40	no	O N	?	Bl.	blue	no	1
	F	1/27/40	no	O N	?	Bl.	blue	no	1
Mother		9/1/09	no	OMN		Br.	blue	yes	
Father		2/23/04	?	?	?	Bl.	blue	?	

ABBREVIATIONS - cf. Tables V and VII.

of J.R. is not known. It is interesting that the proband is L-handed in most activities although the R arm and hand and the L side of the skull appear to be larger than the hemologious structures. It is to noted that in Case I that the proband was natively L-handed as shown in his early tendencies, was changed to R-handedness in school with resulting development of his R arm size equal to the left arm. However, the EEG on L.H. demonstrates native L-handedness. EEG data is not available for J.R. It is unsafe to draw a parallel with the other case (that of L.H.), but one would be tempted to expect an EEG on J.R. to show native R-handedness. Inasmuch as the preceding two cases of persons with SIVC were seen to be R-handed suggesting that handedness and visceral situs are quite independent.

Case V

1. Age: 17 Sex: female Race: Irish-Canadian

2. Complaint: cough and "colored" sputum at 7 years.
treated for tuberculosis.

3. Personal History:

D.K. has not been personally examined by the author. Her history is vague, as taken from the hospital records. Apparently she first reported to the Royal Edward Institute in 1932 with the complaints as above, and has since been carefully supervised, her lung condition being checked by frequent x-ray examinations, her general condition built up by rest and summer camp treatment. The sputum has never been positive. She has had bronchitis, measles, and pertussis but neither pneumonia nor influenza. No pleurisy or sinusitis.

4. Evidence for diagnosis of SIVC:

Without the aid of a physical examination or EKG or barium series the diagnosis rests on the evidence presented by numerous x-ray examinations of the chest over a period of ten years. In that time the stomach has been visualized by means of gas bubbles, and it is seen to lie in the transposed position while the liver is constantly seen on the L. Further studies will be made.

5. Surgical procedures: none.

6. Complications:

Again an admirable case is presented for lipiodol study of the Kartagener syndrome. Here is a girl with a past history of most of the so-called infectious, etiological factors for the production of bronchiectasis. From her first

visit in 1932, throughout her clinical record with few exceptions the note has been made that she has rales which usually disappear on coughing and are more frequent at the L base. Indeed the note was made in her record in June of 1939 that a lipiodol study ought to be made if the rales did not disappear by autumn. The rales were not found in September of 1939 and the lipiodol study has not been done.

7. Handedness: nothing known.

8. Etiology:

a. Family History: no genetic study has been possible on this family because of lack of cooperation. The parents and the surviving brother refuse to report to the hospital for x-ray examination. Physical examination of these patients in their home was not undertaken. The hospital admission of the 19 year old brother include x-rays of the lungs and heart, stating that the heart, aorta and diaphragm, are negative. The parents are apparently unrelated, and there is no history of congenital malformation in the family although pedigree data is not available.

b. Other factors under the heading of Etiology are not known.

9. Hospital Admissions: full story not known.

10. Conclusion:

The above case represents a typical proven case of SIVC in a young girl. There is a strong possibility that this is another Kartagener syndrome. There is a "negative family history" of malformation and situs inversus. No objective study of the family has been possible. The report of this is medically non-contributory in the study of the etiology of SIVC.

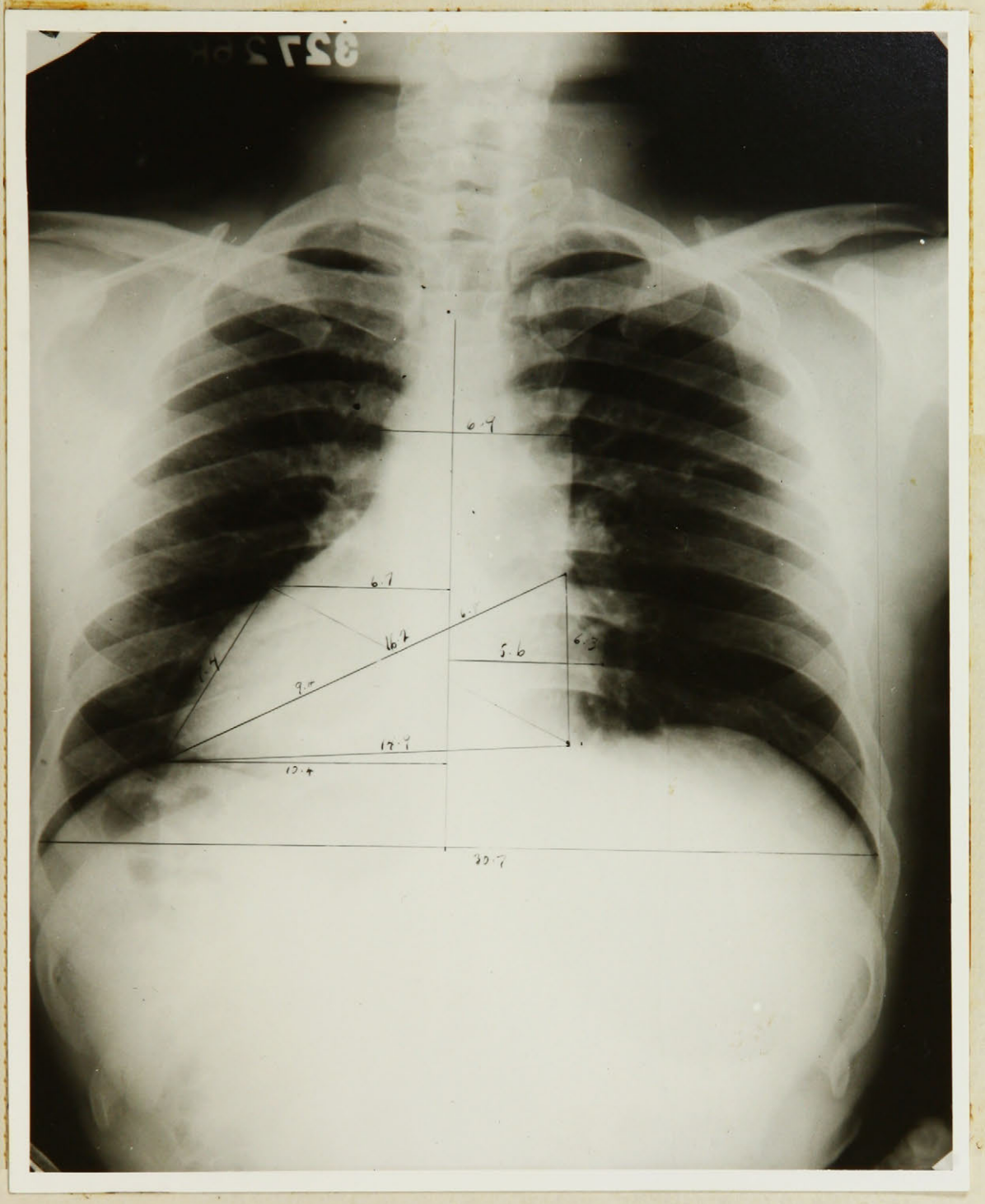
Case VI

This case of a 14 year old girl has been proven by x-ray only. The patient has not been seen by the author, although her home was visited and other members of the family were seen but not examined. The parents were interviewed through an interpreter, and although they agreed to bring the entire family to the hospital for examination, and the means for conveyance were supplied them, the plan never matured. The father and one of the nine children have convergent squint, present from birth. The father states that several members of his family have had a similar condition, but he denies that there have been any malformation or any other cases of situs inversus. The parents state that G.P. was born at home, term birth, normal delivery, and she developed in a normal fashion, had no childhood diseases except measles, and that she has always been healthy. Her one hospital admission, in November, 1941, was for T and A at the Montreal Children's Hospital. The SIVC was discovered by x-ray examination. The parents are both French-Canadians and apparently unrelated. They have always lived in Montreal.

Conclusion: Another case of proven SIVC proven by x-ray examination. No objective data of the sibs and parents is available. No conclusive evidence in regard to etiology has been obtained. There are no symptoms suggesting the usual complications of SIVC. The only value of this case report is to show the occurrence of SIVC in a family which is afflicted with another congenital abnormality which appears

to be hereditary; namely, internal squint; and to show that SIVC occurs in Franch-Canadians of French extraction (cf. also Case III).

Illustration XVII



Chest plate of NMC. Case VII

Dextrocardia of SIVC in patient hospitalized for acute rheumatic fever. The gas bubble in the dextroposed stomach shows clearly. The L diaphragmatic leaf is the higher.

Case VII

Case of N. M. C.

1. Age: 29 Sex: male Race: Italian-Canadian

2. Complaint: rheumatic fever at 27 (1941).

3. Personal History:

The patient was born in 1912 of a 28-year-old mother as her fourth child. He grew up in a fairly normal fashion, never having pneumonia or pleurisy (he does not know whether he had pertussis or measles or influenza, in 1918, or intrathoratic pathological conditions). He is married and had no children and works in a fur dyeing plant.

4. Evidence for diagnosis of SIVC:

a. physical examination: by the methods outlined, the proband shows typical SIVC and no associated congenital anomalies.

b. x-ray: the accompanying illustration of the chest plate, taken during the patient's 1941 admission to the Jewish General Hospital, in Montreal, shows dextrocardia, gas bubble in the stomach on the R and the L diaphragm higher than the R. Another x-ray demonstrates barium in the stomach and in portions of the intestines substantiating the diagnosis of complete transposition.

c. EKG of the heart: usual and reversed leads, shows dextrocardia.

5. Surgical Procedures: none.

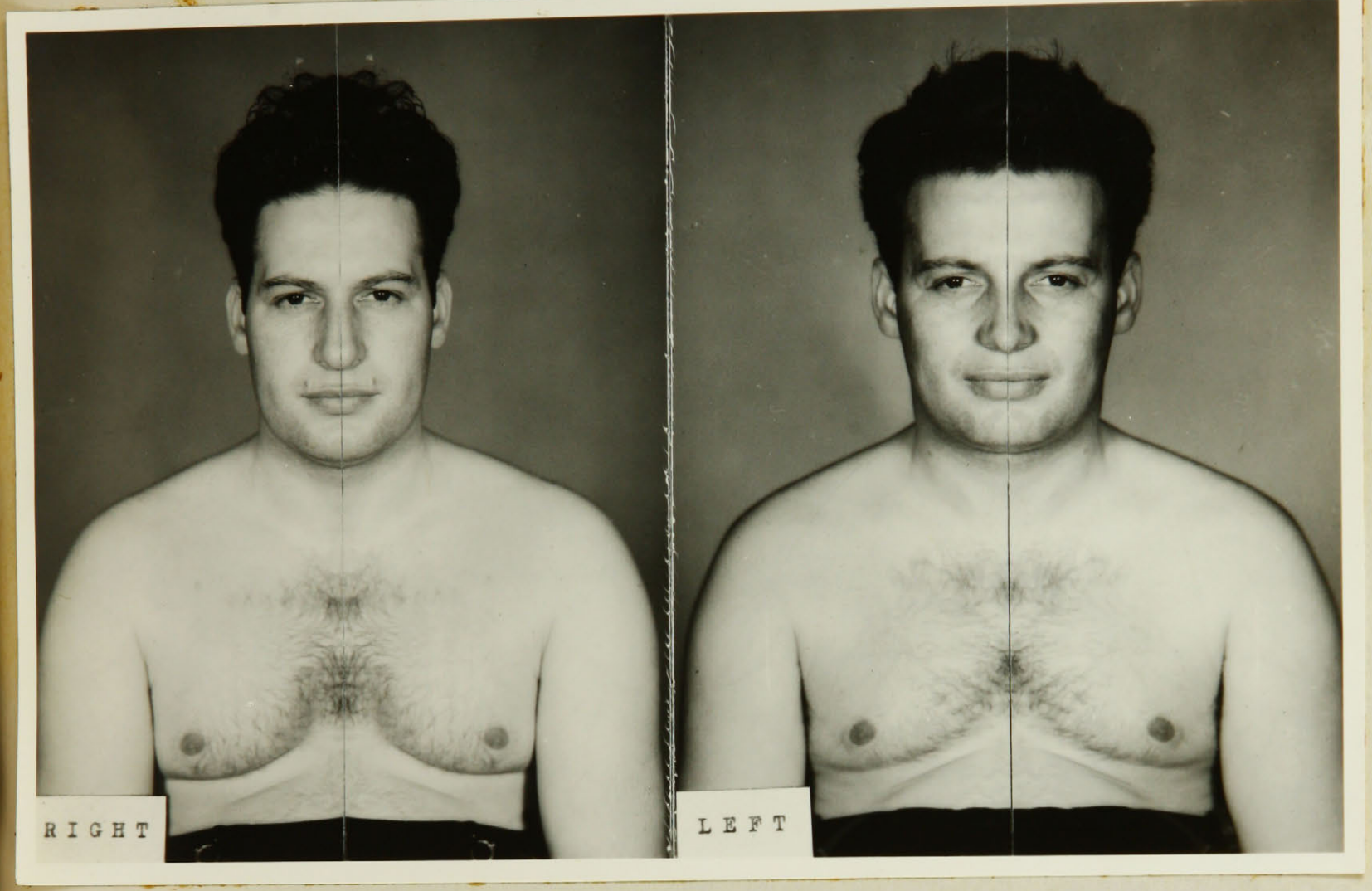
6. Complications:

X-ray of the sinuses in 1941 reveal sinusitis. There have been no symptoms of bronchiectasis (the sinusitis has cleared up). Both testegs are descended. The patient has no hernia and has no signs of congenital heart disease.

7. Handedness:

The patient has no inclination to use his L hand preferentially and writes better with his R hand than with his L hand, as shown in a sample of his handwriting retained by the author.

Illustration XV



Split photograph of R-handed person with SIVC. Case VII

The L side is the larger. This suggests again that the L is the side of cerebral dominance and that the patient is R-handed. The latter observation is confirmed in his handwriting.

8. Etiology

a. Family History: the patient states that no one in his family has ever had a similar condition. There is no record of malformation. The patient's youngest brothers are twins. One of these boys died when he was nine years of age, at home; a sudden death, unexplained. The other boy is still living, at 23. There is no record of twins elsewhere in the family. There is no data available to give a conclusive diagnosis of zygosity or even a suggestive diagnosis thereof. The accompanying chart gives meager information about the sibs and parents.

b. Syphilis: no information available.

c. Alcoholism: denied.

d. Maternal disease during pregnancy: the patient states that his mother had no disease during his pregnancy or any of the other pregnancies.

e. Geographical environment: all the children were born in Montreal and the family has lived there ever since.

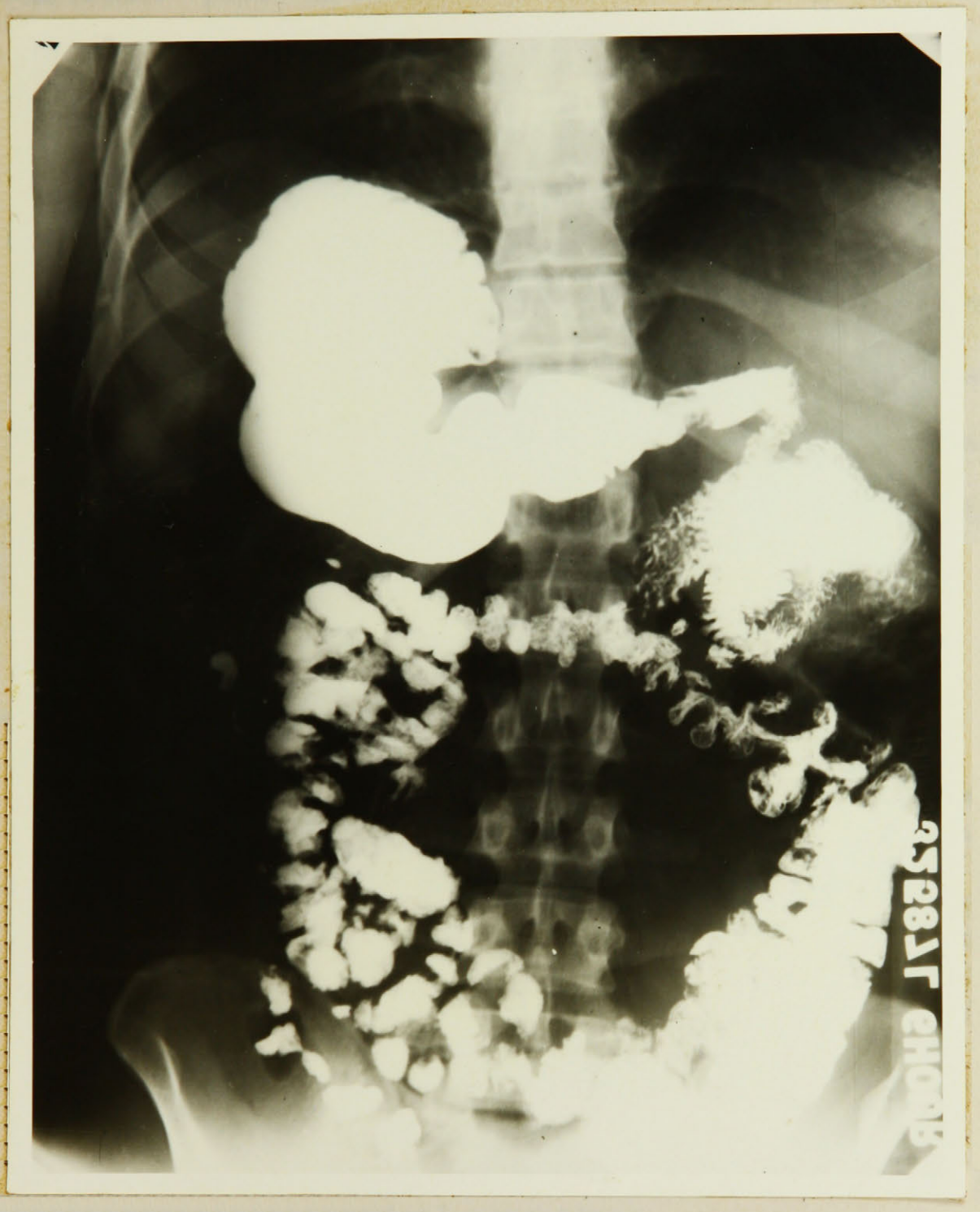
9. Complete Data from all Hospital Admissions:

The proband has had one hospital admission, at the Jewish General, in 1941, when he was diagnosed as a case of rheumatic fever, being treated with digitalis, quinidine, bed rest, whereupon the heart rhythm returned to normal, and the patient was discharged as considerably improved. Data from other hospital admissions has not been obtained. They are listed on this families chart, Table

10. Conclusion:

N. M. C. has complete transposition of the viscera apparently uncomplicated except for rheumatic heart disease with its onset at 27 years.

Illustration XVIII



Barium plate of NMC. Case VII

The dextroposed stomach is clearly shown; the small intestine is seen to be transposed.

Case VIII

Case of E. O. P. - Kartagener Syndrome

1. Age: 29 Sex: male Race: Swedish-Canadian

2. Complaint: pains in chest with chronic cough; question of tuberculosis.

3. Personal History:

The proband was born in western Canada as the third child of his 33-year-old mother. He had pertussis at eight and measles at eight. He has never had pneumonia. He believed he had pleurisy in 1937, and he was diagnosed as having sinusitis in 1932. He has had three operations for nasal polypi. The patient has been in reasonably good health throughout his life but has felt weakened and less capable than usual in handling his job in the last year to two years.

4. Evidence for diagnosis of SIVC:

a. physical examination: by the methods outlined, show typical SIVC and no associated congenital anomalies.

b. x-ray: the accompanying illustration of the chest plate shows typical dextrocardia; the R leaf of the diaphragm, lower than the L; gas bubbles from the stomach on the R; and ectatic bronchæ are revealed by lipiodol injections.

c. EKG of the heart, usual and reversed leads: dextrocardia.

5. Surgical procedures: P and A at ten years; three operations for nasal polypi; no abdominal operations.

6. Complications:

Sinusitis (cf. above), bronchiectasis, yes; demonstrated by lipiodol injection of the lung (cf. illustration). The patient was being investigated at the Royal Edward Institute for tuberculosis because of his complaint of raising sputum, chronic cough, and malaise. He was referred to the author as a case of situs inversus viscerum. On physical examination, dullness was discovered at base of both lungs, more particularly on the left. Typical

Illustration XVI
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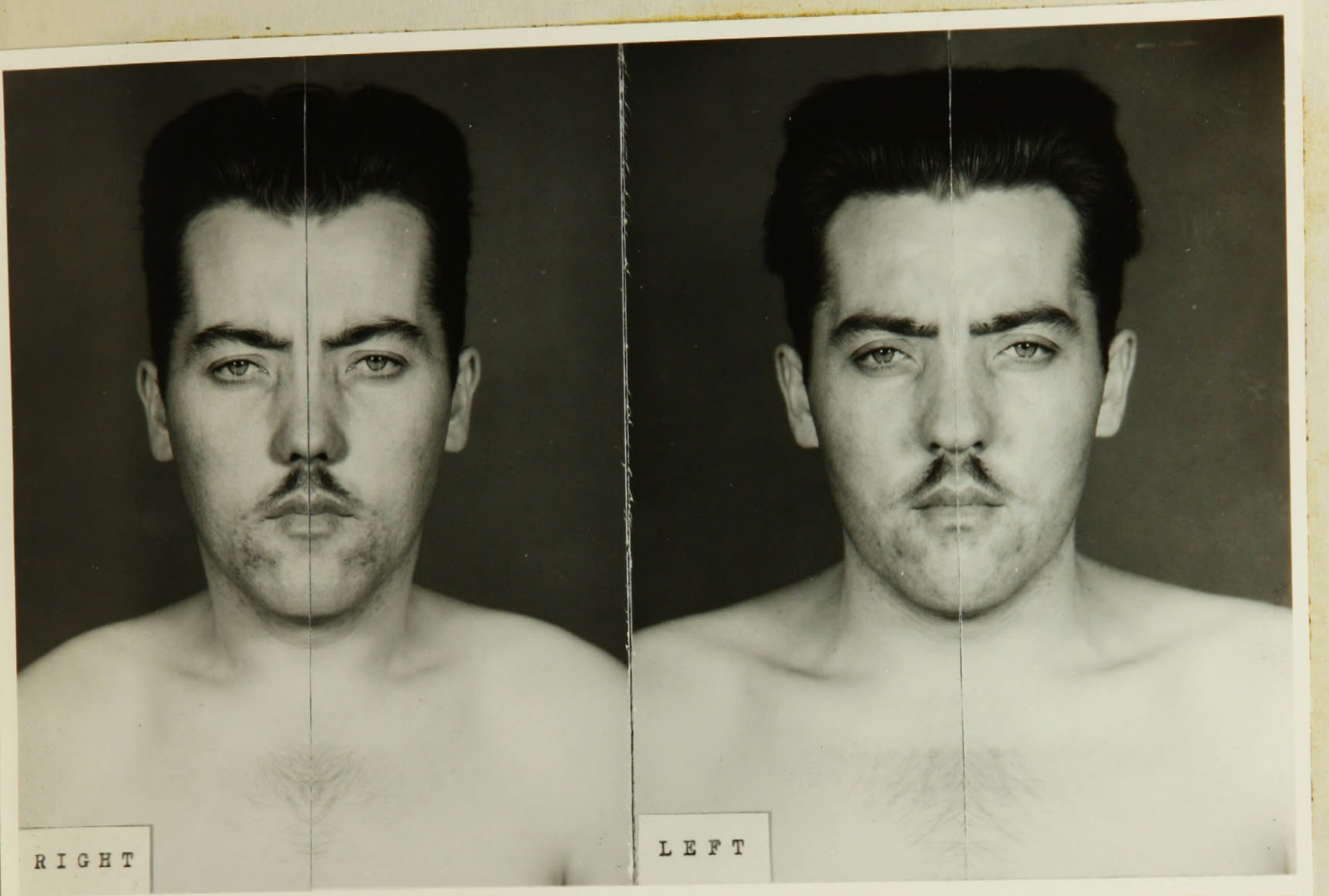


Split photograph of person with SIVC who is R-handed. Case VIII

The face is very symmetrical. An EEG would be particularly useful in this case. (EEG data not available).

auscultatory signs of bronchiectasis were elicited. Preliminary laboratory data were as follows: RBC, 4,450,000; WBC, 6,000; differential, normal; sedimentation rate, first hour eleven; second hour, sixteen; eleven hours, thirty-six. Tuberculin test, one-fifth cc. of one to ten thousand, negative; red in two days. Having this information, it was deemed proper to perform the lipiodol investigation.

This patient has the ~~difficult~~ typical Kartagener syndrome with the combination of bronchiectasis, sinusitis, and SIVC. He has coughed all his life. Investigation at the Edmonton, Alberta Hospital in 1938 included several examinations of his sputum, all of which were negative for tuberculosis. Such examinations were repeated in 1941-1942 at the Royal Edward Institute at Montreal and were again negative for tuberculosis.

The patient is not a cryptorchid, has no hernia, and no evidence of congenital heart disease. (The Edmonton Hospital reports that the proband reported in 1938 with typical symptoms of rheumatic fever, with swollen feet and hands, lung x-ray showing chronic passive congestion, electrocardiograph showing normal rhythm, normal conduction interval, rate of 54.)

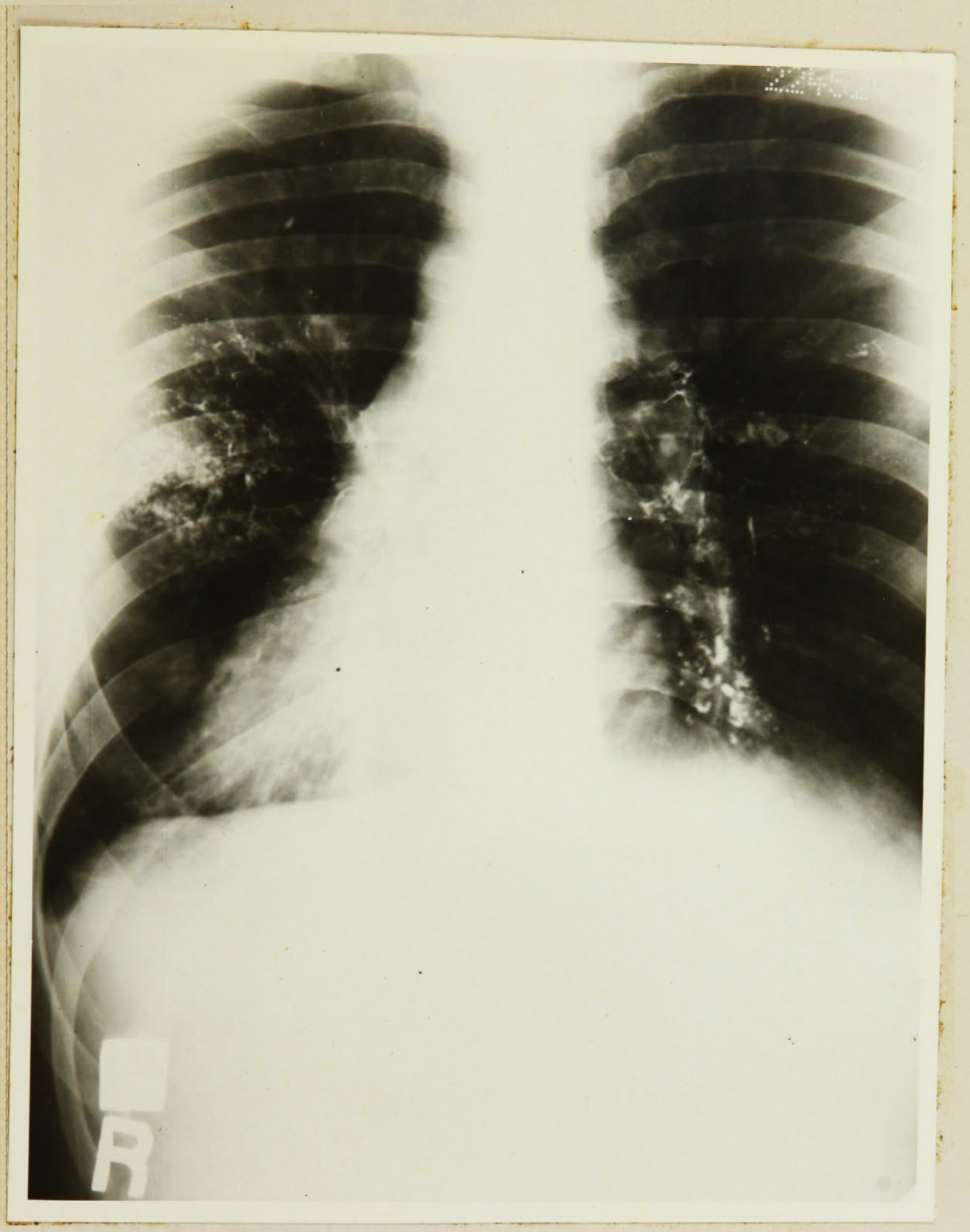
7. Handedness:

The patient is R-handed in all his normal activities. His hand-writing, a specimen obtained with both the R and L hand, is definitely R-handed.

8. Etiology:

a. Family history: the investigation of the sibs and parents of E. O. P. was most unsatisfactory because they are all in the West whereas the proband is in Montreal. Correspondence with a physician in the West revealed that the family is somewhat scattered and that no one physician has seen all members of the family or has carefully investigated with the idea of SIVC in mind. On the other hand, the proband

Illustration XIX



Chest plate of EOP. Case VIII

Lipiodol was introduced to the bronchi, demonstrating the ectasia, seen more especially on the R (in the three-lobed lung). The bilateral distribution of the bronchi is the mirror-image of that in the normal (situs solitus) individual. Dextrocardia is evident.

TABLE X

C.R.	SEX	AGE	EYE COLOR	HAIR COLOR
1	M	34	*blue	*br.
2	F	32	*blue	*br.
3	M	29	blue	br (proband)
4	F	died in infancy, cause unknown		
5	M	26	*blue	*br.
6	M	22	*blue	*br.
7	F	19	*blue	*bl.
8	F	16	*blue	*br.
9	F	13	*blue	*br.

Palmaris longus bilaterally absent in proband negative family history of tuberculosis, heart.disease, and hernia.

*based on anamnestic data only.

is quite certain, in his own mind, that no members of his immediate family have this condition. The accompanying chart of the members of the family shows that a younger brother (No. 5) had pleurisy in 1940, that a younger sister (No. 7) has had bronchitis all her life. These data are suggestive, but they might be misleading. The patient states that his parents are in no way related by blood. The father is 60 in 1942, alive and well. The mother is 62 in 1942, alive and well. Neither has ever had x-rays taken. Sib No. 7, who has complained of bronchitis, has had an x-ray taken, showing no situs inversus (was the film reversed?). There has been no miscarriage in this family. No multiple births for several generations and no malformations. The patient denies that any member of his family has had syphilis, that any member has been addicted to alcohol, that there was any maternal disease during his intrauterine development or during the pregnancy with any of the sibs. The family has always lived in Alberta.

9. Hospital Admissions:

Correspondence with an Edmonton physician has enabled the author to obtain no information in regard to the sibs or parents, but the following information in regard to the proband: admission, November 3, 1938: Dextrocardia; symptoms of rheumatism and rheumatic fever, normal electrocardiogram; admission, February 1, 1939: Dextrocardia; congestive condition at the base of both lungs; complaint of pain in both chests; cough, sputum, and fatigue for three to four weeks.

10. Conclusion:

E. O. P. illustrates that combination of SIVC with sinusitis and bronchiectasis, known as a Kartagener syndrome. There is no evidence of an hereditary eteologic factor.

Case IX

Case P. M. Incomplete SIV

1. Age: 14 months Sex: female Race: English-Canadian

2. Complaint: cyanosis from birth.

3. Personal History:

First-born child, delivered at home of a 22-year-old mother. The child was breast fed until four months; had pertussis at six months. No other infectious disease. There have been two other subsequent pregnancies, ending respectively at six months, dead-born male, and at two months. No cause of death in utero was assigned by the attending physician. All births at home.

The child suffered from cyanosis from birth which was more marked on crying. The first tooth appeared at nine months. The child could not sit up alone, even at fourteen months. It was admitted to the hospital January 18, 1928. Course in the hospital: listlessness and cyanosis from admission; but not the appearance of acute illness. The temperature rose with increased reddening of the throat on January 19; sudden termination with rapid pulse that same day.

4. Evidence for diagnosis of SIV:

a. physical examination: slight precordial bulging was noted on the right half of the chest. Point of maximum impulse was on the right. Relative cardiac diameter extended above the second rib to the right, 8 cm. from the mid-line, to the left, $3\frac{1}{2}$ cm. from the mid-line. The liver was palpable two fingers breadth below the costal margin-on the left presumably (the hospital record from which this information was obtained does not mention which side).

b. x-ray: apparently none taken.

c. EKG of the heart: (the actual report from the hospital record read:) regular rhythm; normal

a-v conduction; inverted t and p in lead one; inverted t and p in lead three; diphasic p wave in lead three; ventricular rate, 120 per minute. "This is not a true mirror picture dextrocardia; curve will be repeated."

On the other hand, Abbott and Moffatt in their report of this case in the Canadian Medical Association Journal in 1929 (reference given page 35 of this paper) interpreted this electrocardiagraphic report (which was not repeated) as definite evidence of situs inversus of the heart.

d. Autopsy report: Mirror picture of dextrocardia without inversion of the aortic arch; vitral aplasia of the systemic vein (on the R) and interauricular defects. Dilatation of the aorta arising from the R ventricle in transposition with the pulmonary artery.

Three spleens were found on the R side. There was incomplete rotation of the liver and the caecum with persistent mesentery. There was partial situs transversus involving the stomach, duodenum, pancreas, and the spleen. The immediate cause of death was functional failure of the heart.

5. Surgical Procedures: none.

6. Complications:

a. Congenital heart disease found at autopsy.
b. multiple spleens

7. Handedness: undetermined.

8. Etiology:

a. Family History: the parents were unrelated by blood. The mother was born in Montreal, August 22, 1904, and was the product of the eleventh pregnancy of her mother. Among her older sibs were two sets of twins, the age and sex and zygosity of whom she does not know. There was no heart disease among her forebears, an older sister suffered from rheumatic fever, but is still alive and well. A younger sister died of rheumatic fever and chorea at the age of 21. On physical examination, the mother proves to be normal and of sound body.

The proband's father states that there is no history of situs inversus or of any malformation in his wife's family or his own forebears. On physical examination, the father proves to be of sound body, with normal visceral situs.

X-ray evidence of situs solitus in both parents of the proband was obtained. From the 1928 hospital record of the proband, a history of heart disease and shell shock in the father was obtained. This the father denies on personal interview. At the time of the Abbott and Moffatt report, 1929, there had been no subsequent pregnancies, but in the interval since 1929, the two miscarriages reported above have occurred.

b. Syphilis: Blood Wassermann on the proband was negative, January 18, 1928: physical examination of the parents, in 1942, reveals no evidence of syphilis.

c. Alcoholism: denied.

d. Maternal disease during pregnancy: the primigravid mother suffered no infectious disease and showed no abnormal symptoms or signs other than albuminuria during her pregnancy.

e. Geographical environment: the parents were born and raised in Montreal and lived in Montreal continuously until the time of the proband's death, at 14 months.

9. Data from Hospital Admissions:

The proband had but one (the terminal) hospital admission. Her sibs had no hospital admissions, being miscarriages which occurred in the home. The father had one hospital admission at the Montreal General Hospital in 1923 for ten days, as the result of an accident on the railroad. This contributed no new information. The mother had no hospital admission, but several of her sibs were admitted to the Royal Victoria Hospital during their life time; however, no new information was contributed by these records.

10. Conclusion:

P. M. represents a case already reported in literature by Abbott and Moffatt (1) as the seventh case from Montreal. Dr. Abbott regarded this as a case of partial situs inversus, not SIVC. The present author has added nothing to the report of

Abbott and Moffatt except further study from the etiologic standpoint, particularly from the hereditary standpoint. The account of two miscarriages subsequent to the pregnancy in which the proband was conceived, and the fact that the first of these miscarriages went to six months and the second only to two months, may suggest to some a luetic basis. The occurrence of two sets of twins among the sibs of the mother, who was one of thirteen children, recalls the suggestion of Newman and others that there is a relationship between twining and the production of visceral transposition.

Here again is a study upon which no conclusions can be based because evidence, once easily obtainable, is no longer available: the situs of the viscera in the two miscarriages, the blood Wassermann of the parents at the time of the birth of their first child, the zygosity of the twins in the family of the mother, and the situs of the viscera in the sibs of the proband's parents.

This case is presented as a family history study in an instance of partial transposition of the viscera.

Case X

This is a man confined to the Verdum Protestant Hospital for mental disease. Complete transposition of the viscera has been demonstrated by the physical examination and by radiology. Since he is a private patient in the clinic, it has been a difficult situation to contact his family and obtain the degree of cooperation necessary to make a complete family history study with a collection of objective data. Nevertheless, this may be regarded as one of the new cases reported in this paper, proven to be SIVC by objective studies, and giving a completely "negative family history" of SIVC, as well as of other malformation.

Case XI

Case of Mrs. R. E. W. R.

1. Age: 41 Sex: female Race: English-American (Virginia)

2. Complaint: (1) acute appendicitis
(2) ssub-acute bacterial endocarditis at 41

3. Personal History:

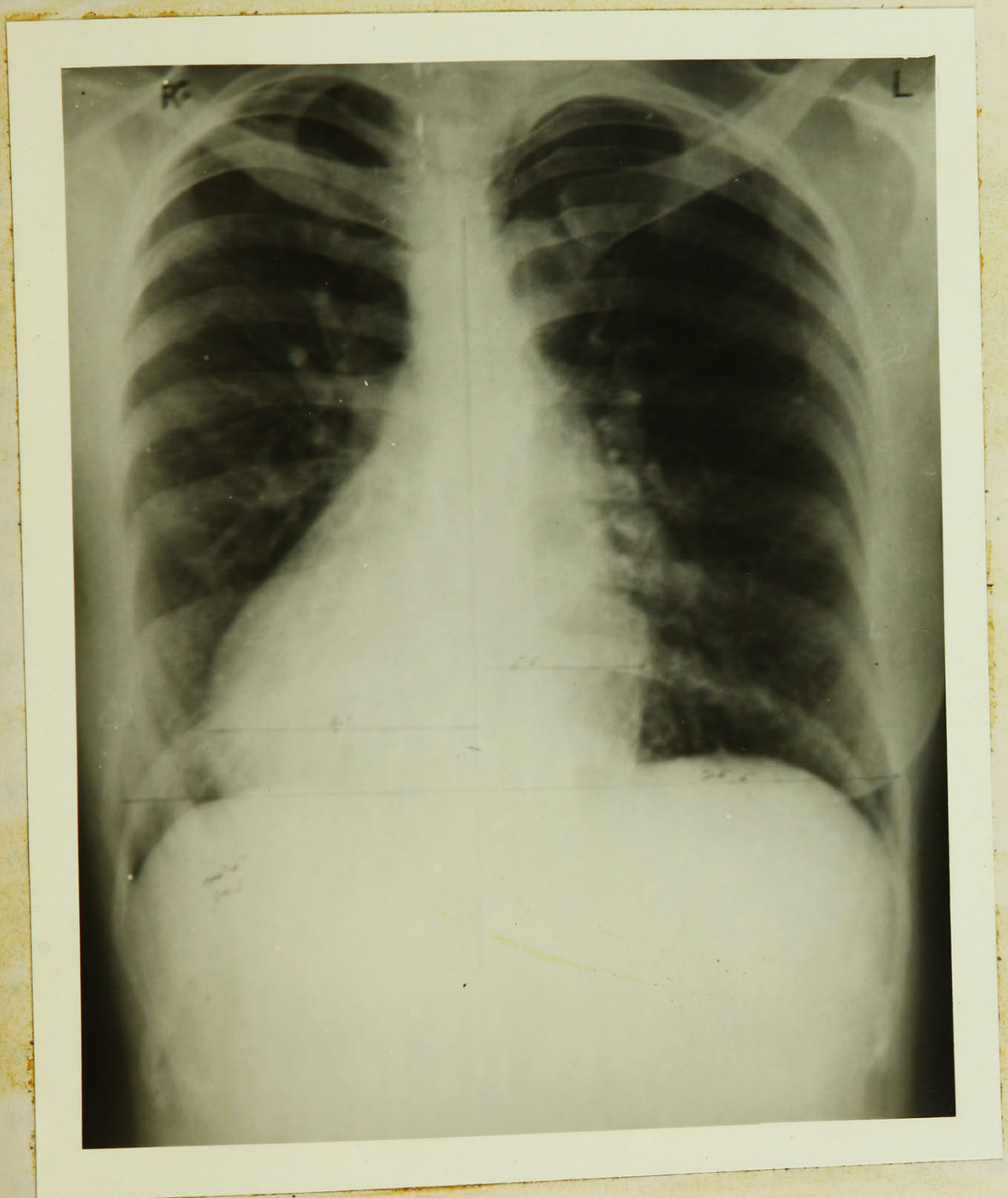
Born as the seventh girl in a family of seven, an apparently normal pregnancy. Her general health has always been good. She had measles, mumps, pertussis, pneumonia, at the age of two years; growing pains frequently as a child; an appendectomy in 1937. There is no record of injuries. There is no record of a chronic cough or of sinusitis.

4. Evidence for diagnosis of SIVC:

a. physical examination: the several past hospital admissions include mention of finding the heart on the right side--dextrocardia. In August of 1941, the PMI was nine cm. to the right of the midsternal line, (nine cm. from the MSL in the right fifth interspace) the left border being three cm. from the MSL. There was a harsh blowing systolic murmur, best heard at the apex, transmitted over the mitral area to the pulmonic region. In October of 1941, the heart was found on the right side, systolic and diastolic murmurs heard over the entire precordium. The former being loud, harsh, and blowing. In August of 1941, the liver edge was palpable under the left costal margin, the spleen not palpable. That same observation was repeated in October.

b. x-ray: previous to the patient's first admission for appendicitis, an x-ray plate was taken after the ingestion of barium, as illustrated, demonstrating the appendix in the left lower quadrant in complete transposition of the gastro-intestinal tract. Another

Illustration XX



Chest plate of REWR. Case XI

Dextrocardia of SIVC in patient hospitalized for sub-acute bacterial endocarditis.

plate, as illustrated, shows dextrocardia.

c. EKG: careful search has failed to reveal record of an electrocardiogram, taken during this patient's three admissions to the hospital (North Carolina Baptist Hospital, Winston-Salem).

5. Surgical Procedures:

On June 1 of 1937, the patient was admitted to the North Carolina Baptist Hospital with the complaint of pains in the left lower quadrant. The patient had been nauseated and had vomited. She stated that the pain had begun in the mid-line, just under her ribs. On physical examination, no rigidity was found, but there was tenderness on palpation in the left lower quadrant more than in any other portion of the abdomen. An immediate diagnosis of acute appendicitis was made. The operation was begun exactly one hour after the patient was admitted to the hospital. An incision in the left inguinal region, corresponding to McBurney's point on the right, was made. The caecum was found on the left side; the appendix, the outer side of the caecum, which was very short and thick, resembling a diverticulum, was removed with difficulty due to adhesions to the bowel. The anesthetic was avertin, five miligrams, plus cyclopropane. The operation required forty minutes. No pathological report on the appendix is found on the hospital record. The patient left the hospital on June 6, the fifth post-operative day.

6. Complications:

There is no record in the patient's history of sinusitis, no symptoms suggesting bronchiectasis, and in view of the early history of joint pain and possible rheumatic fever, there is no reason to conclude that the patient had congenital heart disease as a basis for her sub-acute bacterial endocarditis.

During her second and third hospital admissions, both of them in 1941, the year of her death, she was under the care of a competent internist who interpreted her symptoms and signs and the laboratory data to indicate that the patient had sub-acute bacterial endocarditis (streptococcus virdens) super-imposed upon old rheumatic lesions.

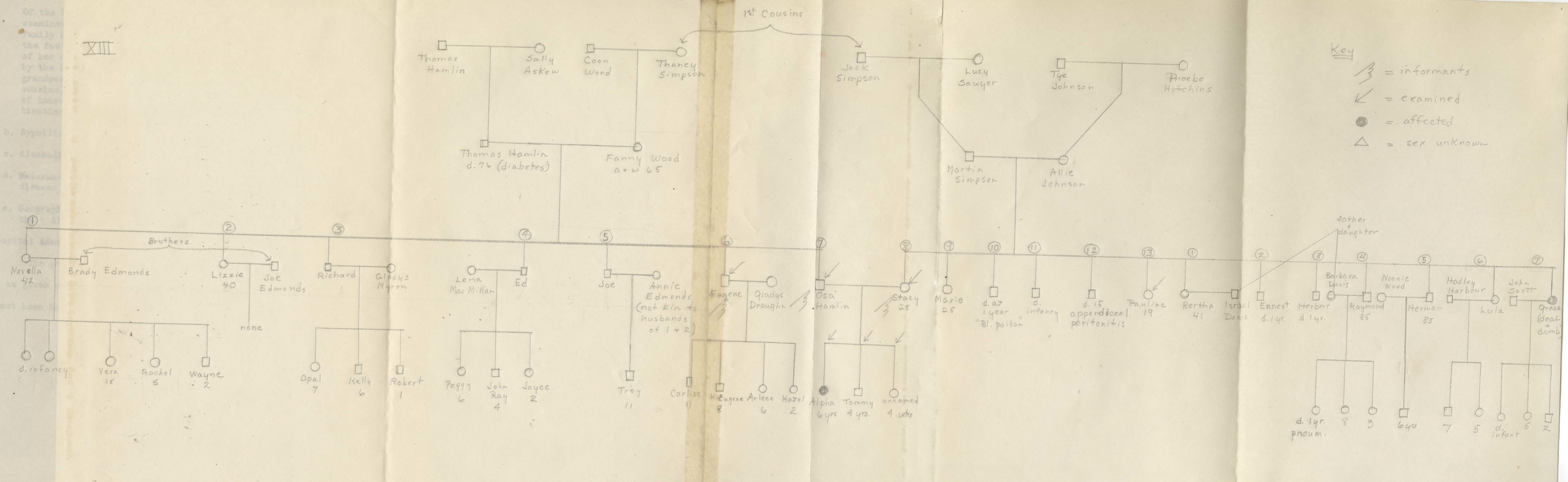
7. Handedness:

No direct evidence of the patient's handedness is available. Her only living sister insists that the patient was always R handed.

8. Etiology:

a. Family History: the proband's father came from Patrick County, Virginia. Her mother, from Louiza, Kentucky. They were apparently not blood relatives. The accompanying pedigree chart gives some information about five dozen members of the proband's family in five generations from anamnestic data. There is no history of congenital malformation or SIVC anywhere in the family. The only surviving sib has been examined and she exhibits situs solitus. It is seen that the proband is the seventh born child. There were no miscarriages. She was married twice. By her first husband, who was not related to her, she had three living children and one miscarriage, the latter occurring between the second and third living child, as shown in the chart. These children are said to be all normal, (situs solitus; none have been examined by the author as yet). The source of the information given on the pedigree chart is Fanny, the fifth born child, who is the only living sib. Another source of information about the family(which does not agree with the information given by Fanny) is the third hospital admission of the proband, wherein the family history is detailed as follows: father died at 45, ruptured appendix and complications; mother died at 55, pneumonia; two sisters died with typhoid fever; one sister died of pneumonia; two sisters died of unknown causes; one sister, living and well. Mother had rheumatism and heart trouble and goiter; one sister died with cancer of the uterus; living sister is obese (this is not true today, one year later; the living sister is of normal weight and size for her age). Marital History: first marriage, duration 9 years; husband died at the age of 30 of unknown cause; two boys, alive and well; one girl, alive and well; one medical abortion because of pyelitis at two months. Second marriage, December 14, 1940; husband, age 48, alive and well.

XIII


1st Cousins
Thomas Hamlin
Sally Askew
Coon Wood
Thancy Simpson
Jack Simpson
Lucy Sawyer
Tye Johnson
Phoebe Hutchins
Thomas Hamlin d. 76 (diabetes)
Fanny Wood a+w 65
Martin Simpson
Allie Johnson
Key
= informants
= examined
= affected
= sex unknown
Brothers
father
daughter
1 Novella 42
2 Brady Edmonds
Lizzie 40
Joe Edmonds
3 Richard
Gladys Myron
4 Lena Mac Millan
Ed
5 Joe
Annie Edmonds (not kin to husbands of 1+2)
6 Eugene
Gladys Draughn
7 Osa Hamlin
8 Stacy 28
9 Marie 25
10 d. at 1 year "Bl. poison"
11 d. infancy
12 d. 15 appendiceal peritonitis
13 Pauline 19
1 Bertha 41
Israel Davis
2 Ernest d. 1 yr.
3 Herbert d. 1 yr.
4 Barbara Davis
Raymond 35
Nonnie Wood
5 Herman 33
6 Hadley Harbour
Lula
7 John Scott
Grace (deaf & dumb)
d. infancy
Vera 15
Rachel 5
Wayne 2
none
Opal 7
Kelly 6
Robert 1
Peggy 6
John Ray 4
Joyce 2
Troy 11
Carlise 11
K. Eugene 8
Arlene 6
Hazel 2
Alpha 6 yrs
Tommy 4 yrs.
unnamed 4 wks
d. 1 yr. pneum.
8
3
6 yrs
7
5
d. infant
6
2

b. Syphilis: there is no record of serological examination of the proband or members of her family. The living sister denies luetic infection anywhere in the family.

c. Alcoholism: denied.

d. Maternal disease in pregnancy: denied.

e. Geographical environment: the family has always lived within an area bounded by Kentucky, North Carolina, and Virginia; the proband spent most of her existence in North Carolina.

9. Data from Hospital Admissions:

The only members of the family known to be confined to the hospital at any time by the surviving sister were Alice and Ruth (the proband). The three admissions of the proband have been consulted and data from them used in the above paragraphs. The record of Alice's one admission, apparently in the year of her death, 1932, is temporarily lost from the hospital record. She is said to have entered the hospital for the correction by surgical means of kyphosis.

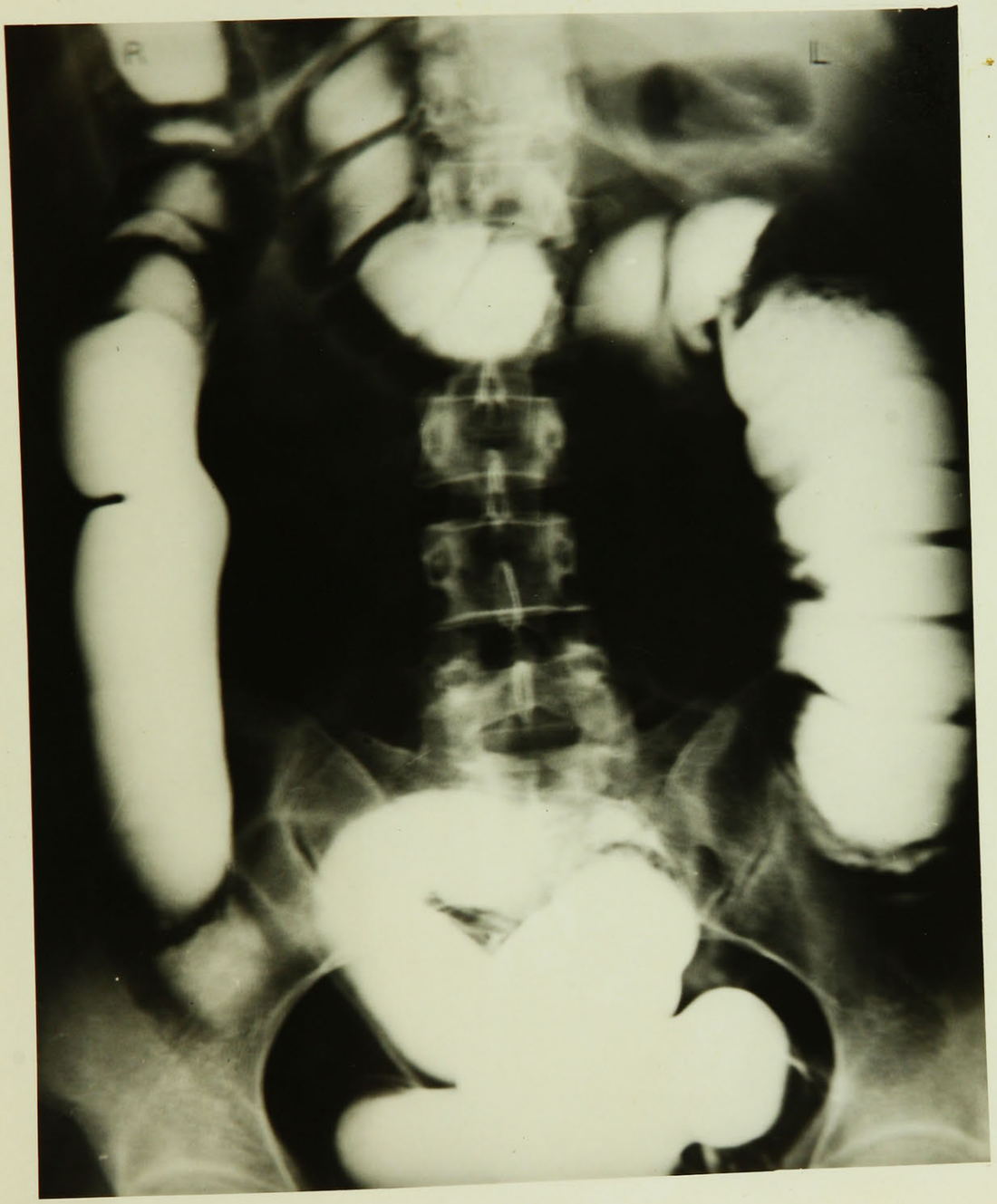
10. Conclusion:

Nothing definitely conclusive can be stated in regard to the etiology of the above case on the basis of the information presented. On the other hand, the case of R. E. W. R. represents a straight-forward story of typical appendicitis, wherein the pain began in the mid-line high in the abdomen and moved down definitely to the location (in the left lower quadrant) of the transposed appendix. The discussion that is current in the literature as to the possibility of independent transposition of the nervous system and the viscera, a supposition made necessary by the reported cases of appendicitis in which the surgeon operating on a case of SIVC went into the abdomen with a right McBurney incision and later found the appendix on the left. is not supported by cases of SIVC which have been

reported from the Orient. The author believes that, may be due to the fact that persons in the Western Hemisphere, especially in the United States, who are unaware of the transposition of their viscera but who are quite aware of the widely celebrated symptoms of appendicitis, are quite apt to report to their doctor not that they have pain in one or other region of their abdomen, but that they have appendicitis. If the story is at all typical, the surgeon consulted is quite apt to procede in routine fashion with a most superficial examination of the patient and a hurried operation. On the other hand, in the Orient where operations for appendicitis are far less frequent and where the public in general is less educated in medical lore, patients are less apt to report to their doctor with a home-made diagnosis and the doctor is more apt to make a thorough examination. It is for this reason that the SIVC of cases reported from the Orient was known before operation and a left lower quadrant incision was always made. In the present case, knowledge of the patient's complete visceral transposition preceded her acute attack of appendicitis. For this reason, the present case cannot be used as an argument against the possibility of the independent transposition of the nervous system and the viscera. This is true because the barium study made prior to the patient's attack of appendicitis had resulted in her being informed of the fact that her appendix was on the left. In consequence, if she were as well speeched in information regarding appendicitis as the average American, she would be apt to report her pain as being from the left lower quadrant.

This case of proven SIVC of unknown etiology was com-

Illustration XXI



Barium visualization of G-I tract of REWR. Case XI

The transposition of the intestines is clearly shown, including the appendix (in the LLQ).

plicated by presence of sub-acute bacterial endocarditis, causing the patient's death (autopsy being refused), probably superimposed upon an old rheumatic lesion of the heart.

Case XII

SIVC Case of Mrs. Elizabeth Dockery

1. Age: 43 Sex: female Race: Surry County, North Carolina

2. Complaint:

(1) Profuse vaginal discharge, one month.

(2) Bleeding of the vagina with cramps, two hours.

(3) Distention of the abdomen, greater than her supposed pregnancy.

3. Personal History:

The patient was the third of three children born to a year old mother at home. She was reasonably well as a child, having pertussis before ten; measles, at ten; no pneumonia, diphtheria. She has never had an attack of appendicitis, and she has had no operations. She has not been troubled with cough or sputum. Until the last two or three years, she has never had sinus trouble, but during the last two or three years she has been troubled with headaches and discharges, medically diagnosed as sinusitis. Before the age of six, the child's dextro-posed heart was discovered by a physician, who was treating her for convulsions.

4. Evidence for the diagnosis of SIVC

a. physical examination: by the methods outlined, shows typical SIVC and no associated congenital anomaly.

b. x-ray: chest plate shows typical dextrocardia, the right leaf of the diaphragm lower than the left; a gas bubble in the stomach on the right. The liver is clearly visible on the left; barium x-ray: SIVC

c. EKG of the heart, usual and reversed leads: dextrocardia.

5. Surgical Procedures: No intra-theracic or intra-abdominal procedures.

6. Complications: The patient denies any cough or sputum; sinusitis for the last three years, treated by a reliable

physician. There seems to be no indication for lipiodol investigation of the lungs, on the basis of symptoms.

7. Handedness:

The patient sews and writes with her right hand. She has never been adept with her left hand.

8. Etiology:

a. Family history: The accompanying pedigree chart, showing 25 persons from five generations with the proband as the only affected person, contributes very little to this case. Eventually, all the proband's children and grandchildren will be examined as well as her one living brother and her mother. There is no indication of any inbreeding.

b. Syphilis: No information.

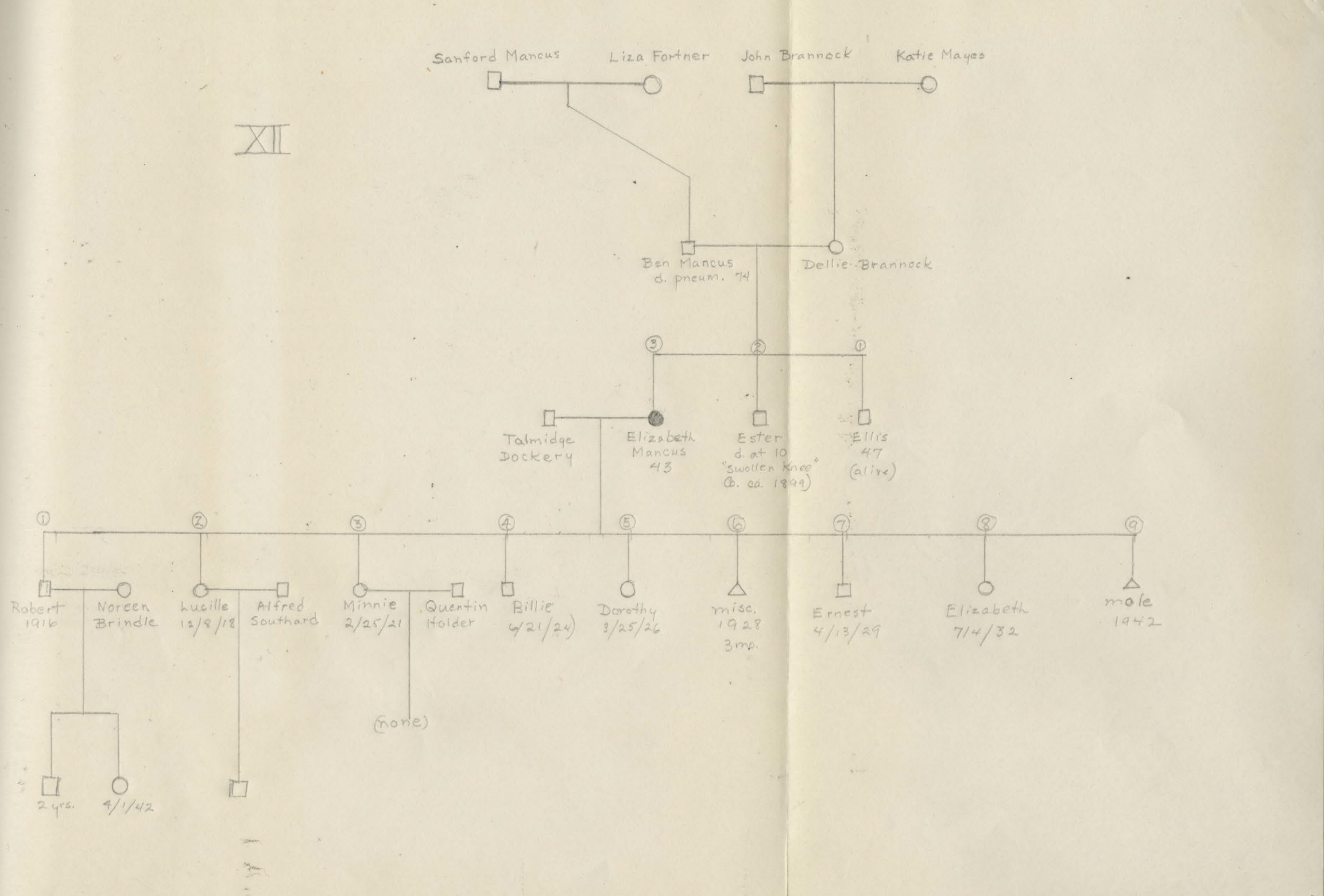
c. Alcoholism: No information.

d. Maternal disease during pregnancy: knowledge of this factor awaits the occasion of an interview with the proband's mother.

e. Geographical environment: the proband's family has has always lived in Surry County, North Carolina.

9. Hospital Admissions:

The patient has had but two hospital admissions, both in 1942 at the Elkin Hospital; the first one, on June 30, when her condition was diagnosed as a normal eight-weeks pregnancy. The second one, in August, 1942, when the diagnosis was toxemia of pregnancy with hydatidiform mole.


Sanford Mancus
Liza Fortner
John Brannock
Katie Mayes
XII
Ben Mancus
d. pneum. 14
Dellie Brannock
3
2
1
Talmidge Dockery
Elizabeth Mancus
43
Ester
d. at 10
"swollen knee"
(b. ca. 1899)
Ellis
47
(alive)
1
2
3
4
5
6
7
8
9
Robert
1916
Norcen Brindle
Lucille
12/8/18
Alfred Southard
Minnie
2/25/21
Quentin Holder
Billie
6/21/24
Dorothy
3/25/26
misc.
1928
3mo.
Ernest
4/13/29
Elizabeth
7/4/32
male
1942
(none)
2 yrs.
4/1/42

SIVC Case of Alpha Hamlin

1. Age: 6 years Sex: female Race: Surry County, N. C.

2. Complaint: tonsillitis at six years.

3. Personal History:

The girl was born in Dobson, Surry County, North Carolina, in 1936. She was the first pregnancy of her 22 year old mother. Her delivery was at home. The child has progressed to her sixth year with almost no illnesses, having measles and diphtheria in the winter of her sixth year. She has not had pneumonia or pertussis. On August 8, 1942, the 44 pound, six year old child was admitted to the Hugh Chatham Hospital in Elkin, North Carolina, for tonsillectomy. At this time, the house officer noted the dextrocardia, and made a clinical diagnosis of SIVC.

4. Evidence for diagnosis of SIVC:

a. on physical examination, the heart was found dextroposed, the stomach and liver transposed.

b. x-ray of the chest and abdomen: dextrocardia and SIVC; barium examination of the G-I tract: SIVC.

c. EKG of the heart with the usual and with reversed leads: dextrocardia.

5. Surgical Procedures: none.

6. Complications: none.

7. Handedness:

The child has begun school and writes with her right hand. The parents have never noted any tendency for left-handedness.

8. Etiology:

a. Family history: The accompanying pedigree chart of the Hamlin family for four generations shows only the proband to be affected. Arrows point to those members of the family who have been examined by the author:

Of the 71 individuals charted, only seven have been examined by the author. The worthlessness of a "negative family history" of this condition is illustrated by the fact that the parents of the proband were unaware of her dextrocardia until informed in August of 1942 by the house officer at the Elkin Hospital. The great-grandparents of the proband include two, who were first cousins, as shown on the pedigree chart. This degree of inbreeding is very slight. The result of hemogglutination tests is shown in table

b. Syphilis: no data.

c. Alcoholism: there is no history of alcoholism.

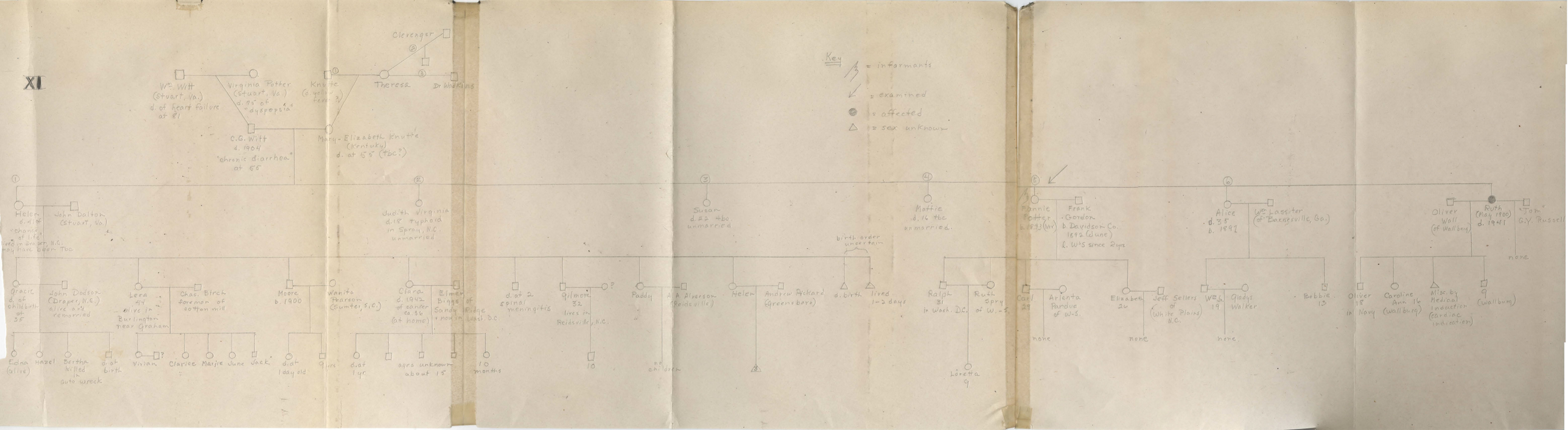
d. Maternal disease during pregnancy: mother denies any disease during pregnancy.

e. Geographical environment: the parents have lived all their lives in Surry County, near Dobson.

9. Hospital Admissions:

The proband's only hospital admission was in August, 1942, as given above. Other members of the immediate family have not been hospitalized.

XI


Clerenger
Wm. Witt (Stuart, Va.) d. of heart failure at 81
Virginia Potter (Stuart, Va.) d. 95 of "dyspepsia"
Knuttie (d. yellow fever)
Theresa
Dr Wheelkins
C.G. Witt d. 1904 "chronic diarrhoea" at 55
Mary - Elizabeth Knutte (Kentucky) d. at 55 (TBC?)
Key
= informants
= examined
= affected
= sex unknown
1
2
3
4
5
6
Helen d. 41 of "chronic" at life lived in Draper, N.C.; may have been TBC
John Dalton (Stuart, Va.)
Judith Virginia d. 18 typhoid in Spray, N.C. unmarried
Susan d. 22 tbc unmarried
Mattie d. 16 tbc unmarried
birth order uncertain
Gracie d. at childbirth at 35
John Dodson (Draper, N.C.) alive and remarried
Lera 44 alive in Burlington near Graham
Chas. Birch foreman of cotton mill
Moore b. 1900
Wanita Pearson (Sumter, S.C.)
Clara d. 1942 of cancer ca 36 (at home)
Elmer Biggs of Sandy Ridge now in Wash. D.C.
d. at 2 spinal meningitis
Gilmer 32 lives in Reidsville, N.C.
Paddy
A.A. Alverson (Reidsville)
Helen
Andrew Pickard (Greensboro)
d. birth
lived 1-2 days
Ralph 31 in Wash. D.C.
Ruth Spry of W.-S.
Loretta 9
Edna (alive)
Hazel
Bertha killed auto wreck
d. at birth
Vivian
Clarice
Marjie
June
Jack
d. at 1 day old
9 lives
d. at 1 yr
ages unknown about 15
10 months
10
no children
3
Connie Potter b. 1893 (WS)
Frank Gordon b. Davidson Co. 1892 (June) d. W-S since 21yr
Alice d. 35 b. 1897
Wm Lassiter (of Barnesville, Ga.)
Oliver Wall (of Wallburg)
Ruth (May 1900) d. 1941
"Tom" G.Y. Russell
Carl 23
none
Arenta Pardue of W-S.
Elizabeth 20
none
Jeff Sellers of (White Plains) N.C.
Wm 19
none
Gladys Walker
Bobbie 13
Oliver 18 in Navy
Caroline Ann 16 (Wallburg)
Misc. by Medical inspector (carcinoma indicated)
9 (Wallburg)
none

Summary of Case Reports

In the foregoing presentation of cases an attempt is made to bring out those points that make the study of situs inversus a significant one, and, at the same time, to provide material which may serve as a clue to the etiology of this condition. Of the thirteen cases, twelve were original, previously unreported ones. A summary of some of the salient features of these cases is provided in the accompanying table. In studying this table, it must bourne in mind that Case IX is not complete situs inversus. There were five males and eight females. The age range was from ten months to forty-three years. Five or six racial groups were represented. The same range of complaints as in the normal population brought these patients to the physician, but the series is too small to state whether the various complaints were occurring with normal frequency. It is to be noted, however, that there were several cases with heart disease. Nine of the thirteen were definitely established as SIVC on a basis of the data collected by physical examination, x-ray, and electrocardiogram. Two were based on x-ray examination only. One was based on a combination of physical examination and x-ray, and the remaining one was established as a case of incomplete situs inversus by post mortem examination. In the complications occurred rheumatic heart disease twice, and one patient with sub-acute bacterial endocarditis superimposed on a probable rheumatic heart disease. One case was definitely bronchiectasis and another case was questionable bronchiectasis. One case was definite congenital heart disease. One case was cryptorchidism at birth, corrected during the first year. Handedness was

Table X I

Case	Age	Race	Chief complaint	Proof	Complication	Handedness
I	27	Scotch-Canad.	pneumonia at 26	PX, x-ray EKG	none (bronchiectasis ?)	R (L by EEG)
II	37	Ital.-Canad.	rheumatic fever at 30	PX, x-ray EEG	rheum. fever	R
III	1	Fr.-Canad.	marasmus	PX, x-ray EEG	cryptorchid at birth	R
IV	10	Scotch-Canad.	sinusitis	PX, x-ray EEG	none	R
V	17	Irish-Canad.	? tuberculosis	x-ray only	? bronchiectasis	(unknown)
VI	14	Rr.-Canad.	tonsillitis	x-ray only	none	(unknown)
VII	29	Ital.-Canad.	rheumatic fever at 27	PX, x-ray EKG	rheum. fever	R
VIII	29	Swedish-Canad.	bronchiectasis (not tbc!!)	PX, x-ray EKG	bronchiectasis	R
X	adult	unknown-Canad.	mental disease	PX, x-ray EKG	none	(unknown)
XI	41	Eng.-American	acute append., endocarditis	PX, x-ray	append., endocarditis	R (known?)
XII	43	Amer., N.C. (Surry Co.)	Hydatid mole	PX, x-ray EKG	none	R
XIII	6	ditto	tonsillitis	PX, x-ray EKG	none	R
IX	1	cyanosis	Eng.-Canad.	autopsy (incomplete SIV)	CHD	(unknown)

Abbreviations

PX - physical examination, EKG - electrocaridogram,
N.C. - North Carolina, Co. - county, append. - appendicitis.

determined in eight of the thirteen cases, only one of those eight being L-handed, as determined on anamnestic data and hand-writing. Only one of those thirteen was tested by EEG revealing that this subject, although R-handed in general activities, demonstrates R cerebral dominance, indicating native L-handedness.

There is no reason to believe from the data given in the foregoing cases that there is an hereditary factor in the etiology of situs inversus viscerum. On the other hand, there is no reason in such a small series of cases to suppose that the foregoing constitutes evidence that SIVC is not hereditary. An alternative hypothesis cannot be established on a basis of this series of cases.

Case VIII illustrates the importance of recognizing SIVC and its usual complications. After the author's establishment of the diagnosis of the Kartagener syndrome, the patient was no longer required to report to the tuberculous clinic. Case V may be another such case, the girl still reporting regularly to the tuberculous clinic and no lipiodol examination ever having been made. Case XI illustrates nicely the importance of recognizing visceral situs before operation, in fact before the onset of acute symptoms in a surgical condition. These are the clinically significant features of SIVC and aspects of the above case reports.

VII.

SUMMARY AND CONCLUSIONS

A. Summary

A complete review of approximately nine hundred extant articles on situs inversus viscerum completus (SIVC) in man, the preparation of a complete bibliography of the casuistic literature 1925 through 1941, the preparation of a comprehensive outline which embodies important headings for all the items of knowledge which still require investigation, and the report of six new cases constitute the original work of this thesis. An attempt to relate SIVC to other physiological and pathological forms of asymmetry in man and other animals is made. The new cases reported and one additional case previously reported (proven to be partial and not complete situs inversus) are studied from the standpoint of etiology and the possible significance to clinical medicine and general biology that a careful study of these cases may indicate.

B. Conclusion

1. SIVC is a good subject for medico genetic study because:

   a. it is a distinct nosological entity which may be uniquivocably diagnosed and as such postly approximates the Medelian postulate of a "unit character".

   b. this character is present at birth; consequently, it is possible to determine its presence or absence at all ages with absolute certainty--no difficulty about the age of onset.

   c. it is a rare character which is of interest to lay people as well as to medical people and there is no disgrace connected with the occurrence of this trait in a family. For these reasons it is not difficult to arouse initial interest in lay and professional circles.

d. there is considerable matter of theoretical and practical importance related to SIVC as a human trait.

2. The extensive literature on SIVC practically exhausts the field of anatomical studies, but leaves much room for highly important work in physiology, pathology, etiology, and surgical pathological physiology of SIVC.

3. Past work on the genetics of SIVC has been almost negligible and of poor scientific quality. The best work indicates that SIVC may in certain cases be inherited as a single Mendelian autosomal recessive for the method of production of SIVC is not certainly known. The twelve cases herein reported are believed by the author to be more completely studied from the etiologic standpoint than any reported in the literature. Nevertheless, this statistically small but nonetheless unusually large series of cases of this supposedly rare trait, supplies no definite clue as to the etiology of this condition. The most likely hypothesis is that of developmental arrest at the time of situs termination, but whether arrest depends upon hereditary factors ever, sometimes, or never remains to be conclusively proven.

5. No conclusions in regard to heredity or etiology can be given as a result of the studies reported in this paper.

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The Reference List of this paper consists of two parts:

PART I - A complete casuistic bibliography of Situs Inversus Viscerum Completus from 1925 -1941 inclusive.

PART II- References cited in paper, but not included in Part I.

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