ON THE NATURE OF SYNDROME DELINEATION

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Perhaps half of all patients with multiple abnormalities have known, recognized syndromes. The other half represent unknown entities that need to be further delineated. The significance of syndrome delineation cannot be overestimated. As an unknown syndrome becomes delineated, its phenotypic spectrum, its natural history, and its risk of recurrence become known, allowing for better patient care and family counseling.

The process of syndrome delineation is discussed in terms of unknown genesis syndromes of the provisionally-unique and recurrent-pattern types, and known-genesis syndromes of the pedigree, chromosomal, biochemical-defect, and environmentally-induced types. Several special syndrome categories are defined, including the chance syndrome, variant additive syndrome, association syndrome, exceptional chromosomal syndrome, and exceptional monogenic syndrome. Finally, a population definition of a syndrome is developed.

INTRODUCTION

The term syndrome has been used in a variety of different ways. It has been applied to collections of signs, to groups of symptoms, and to mixed assortments of signs and symptoms. The syndrome label has been attached to both specific and nonspecific entities. For some clinicians, the term refers to a group of manifestations when the cause is poorly understood, the term disease being reserved for disorders of known genesis. For others, syndrome and disease are equivalent concepts.[1] Still others use the term for multiple anomalies of genetic origin. The designation has even been employed for specific laboratory findings [2] as well as for apparently unconnected clinical findings.[3] A definitive history of the term syndrome and its usages has yet to be written. The word syndrome is derived from Greek and literally means "a running together." For our purposes in this article, *a syndrome will be defined simply as two or more abnormalities in the same individual.*

The view of syndrome delineation developed here is based upon the work of Opitz et al. (1969). However, it differs in a number of respects. First, more complete explication of syndrome delineation is provided. Second, the discussion is generalized from malformation syndromes to include all dysmorphic syndromes.[4] Finally, the terminology proposed here differs from that used by Opitz et al. (1969).

[1] Disease and syndrome were equivalent concepts for Thomas Sydenham, according to Kogoj (1956).

[2] In the Guillain-Barré syndrome, the diagnosis is based upon an acute infective polyneuritis with a high cerebrospinal fluid protein, but an absence of cells.

[3] The Gerstmann syndrome is characterized by inability to recognize the fingers, left-right disorientation, acalculia, and agraphia. These apparently unconnected findings have been observed with lesions of the parietal lobe as well as with lesions of the frontal lobe.

[4] Dysmorphic syndromes include dysmetabolic syndromes, dyshistogenetic syndromes, malformation syndromes, and deformation syndromes. These are discussed in detail by Herrmann and Opitz (1974) and Cohen (1976).

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The significance of syndrome delineation cannot be overestimated. As an unknown syndrome becomes delineated, its phenotypic spectrum, its natural history, and its risk of recurrence become known, allowing for better patient care and family counseling. If the phenotypic spectrum is known, the clinician can search for suspected defects that may not be immediately apparent, such as a hemivertebra in the Goldenhar syndrome. If a certain complication can occur, such as a Wilms tumor in the Beckwith-Wiedemann syndrome, the clinician is forewarned to monitor the patient with intravenous pyelograms. Finally, if the recurrence risk is known, such as the 25% risk for the Carpenter syndrome, the parents can be counseled properly about future pregnancies. This is especially important if the risk is high and the disorder is handicapping or disfiguring, or has mental deficiency as one component, or has a dramatically shortened lifespan.

THE PROCESS OF SYNDROME DELINEATION

The process of syndrome delineation can be divided into the following stages:

(A) Unknown-genesis syndrome
(A.1) Provisionally-unique-pattern syndrome
(A.2) Recurrent-pattern syndrome

(B) Known-genesis syndrome
(B.1) Pedigree syndrome
(B.2) Chromosomal syndrome
(B.3) Biochemical-defect syndrome
(B.4) Environmentally-induced syndrome.

In an unknown-genesis syndrome, the cause is simply not known. There are two types of unknown-genesis syndromes.

A.1. *In a provisionally-unique-pattern syndrome, two or more abnormalities are observed in the same patient such that the clinician does not recognize the overall pattern of defects from his own experience, nor from searching the literature, nor from consultation with the most learned colleagues in the field* (Fig. 1-3). The probability that these abnormalities occur in the same patient by different causes acting independently becomes less likely the more abnormalities the patient has and the rarer these abnormalities are individually in the general population.

Obviously, if a second example comes to light, the condition is no longer unique. A provisionally-unique-pattern syndrome is a one-of-a-kind syndrome *to a particular observer at a particular point in time.* There may be a nineteenth-century description of a similar instance that escapes his attention. There may also be many instances of the syndrome in different parts of the world that remain as yet unrecognized. Thus, many syndromes appear to be unique at the time the initial patient is discovered, but are no longer unique when two or more examples become known. On the other hand, some syndromes may be truly unique; this possibility is explored later in the text.

In clinical genetics, there is a widely held view that a recurrent pattern of abnormalities in two or more individuals constitutes a syndrome, but that a provisionally-unique pattern of abnormalities in a single patient cannot be accorded syndrome status. Clinicians who subscribe to this notion belong to the "it-takes-two-or-preferably-more-to-make-a-syn-

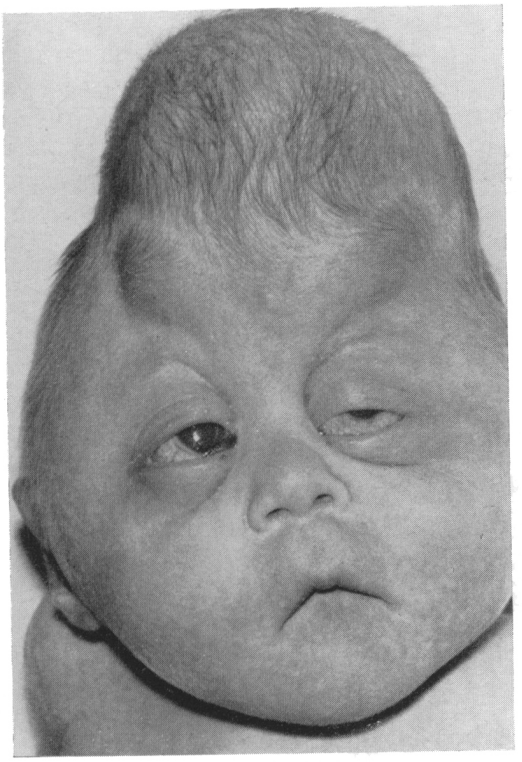

Fig. 1

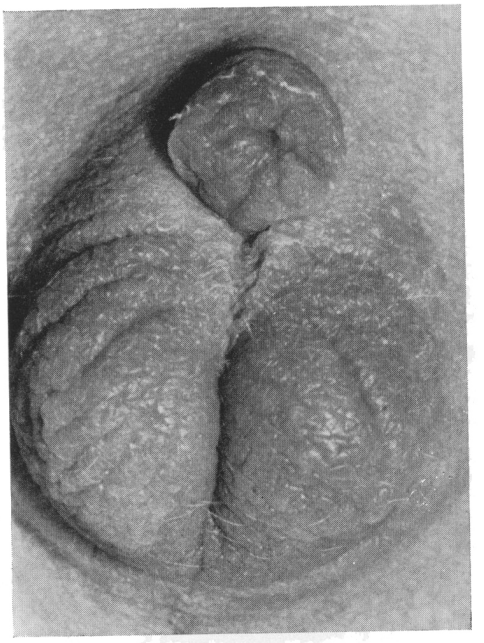

Fig. 2

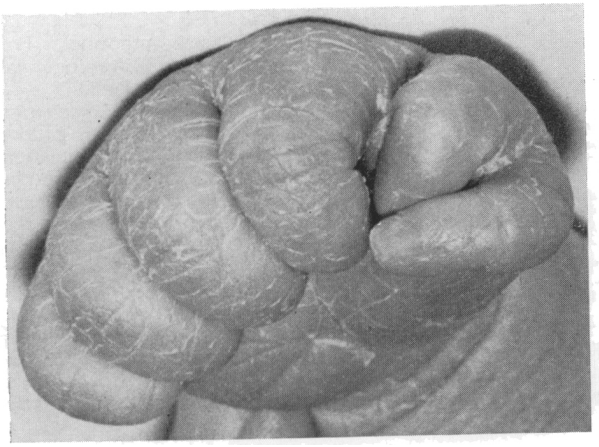

Fig. 3

Figs. 1-3. An example of a provisionally-unique-pattern syndrome consisting of a cloverleaf skull malformation, preaxial polydactyly, micropenis, cryptorchidism, and bifid scrotum. To date no other cases are known.

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drome" school. Their reasoning is fallacious: "a syndrome is a syndrome is a syndrome." To take an instructive example, paleontologists sometimes define a whole species on the basis of a single fossil specimen. *One wants a definition that states clearly, "item x belongs to class y or it does not," irrespective of how many x's there are and, in formal logic, a class may have as few as one member — or even none!* Thus, the term syndrome can apply to a one-of-a-kind condition as well as to a many-of-a-kind condition. The concept of a provisionally-unique-pattern syndrome has been recognized and appreciated by Opitz et al. (1969) and Warkany (1971*a*, 1971*b*), but is conspicuously absent from syndrome textbooks (Gorlin et al. 1976, Smith 1976, Holmes et al. 1972) and even from reports of a meeting which attempted to deal with problems of syndrome nomenclature and classification (Anonymous 1975*a* and 1975*b*, Smith 1975).[5]

There is a definite need for a term such as provisionally-unique-pattern syndrome.[6] In a large study of newborn infants with multiple anomalies (malformation syndromes), only 40% had known, recognized entities (Marden et al. 1964). The other 60% represented one-of-a-kind syndromes that needed to be further delineated. Thus today, on the average, perhaps half of all dysmorphic syndromes seen by clinical geneticists may be provisionally-unique-pattern syndromes. Such a large and important class of patients merits its own special designation. Even those clinicians who belong to the "it-takes-two-or-preferably-more-to-make-a-syndrome" school recognize provisionally-unique-pattern syndromes in practice if not philosophically. For example, such a clinician may say to a parent, "your child has a pattern of abnormalities that we do not recognize"; in this statement, the concept of a provisionally-unique-pattern syndrome is certainly evident covertly if not overtly.

Ideally, all provisionally-unique-pattern syndromes should be published. In practice, they are usually filed away and hardly ever published because their significance is a mystery to clinicians and to journal editors alike.[7] However, the publication of a provisionally-unique-pattern syndrome is like an advertisement with a red flag (Figs. 1-3); it reaches a large audience, which may allow one or more clinicians to react by publishing similar cases. When this happens, the process of syndrome delineation is underway.

A.2. *A recurrent-pattern syndrome can be defined as a similar or identical set of abnormalities in two or more unrelated*[8] *patients* (Figs. 4 and 5, Table 1). The same abnormalities observed

[5] Even some many-of-a-kind disorders do not rate syndrome status, according to some authorities. For example, an *association* has been defined as "a recognized pattern of malformations *which currently is not considered to constitute a syndrome...*" (Anonymous 1975*a* and 1975*b*, Smith 1975) (emphasis ours).

[6] To our knowledge, the only other designation proposed for a similar concept is the term *physical-examination syndrome* introduced by Opitz et al. (1969). We prefer not to use the term for two reasons. First, it does not connote anything characteristic of the class of syndromes with which we are dealing. A physical examination is necessary to describe *any* syndrome, even a well-delineated one of known etiology, such as the Hurler syndrome. Second, since the term *physical-examination syndrome* was introduced in 1969, neither the term nor, more importantly, the concept has been widely accepted or used by clinical geneticists other than the Madison group.

[7] The mission of the new journal *Syndrome Identification* is to publish provisionally-unique-pattern syndromes to allow clinicians to react by publishing similar cases if they exist. This journal is one of the few outlets for such activities.

[8] An occasional patient *may be related* within a large syndrome sample, yet the delineation status remains at the level of a recurrent-pattern syndrome. For example, there are hundreds of sporadic instances of the Rubinstein-Taybi syndrome and rare instances of affected sibs, yet the condition is still a recurrent-pattern syndrome. To argue in favor of either polygenic or autosomal recessive inheritance seems to be overly simplistic.

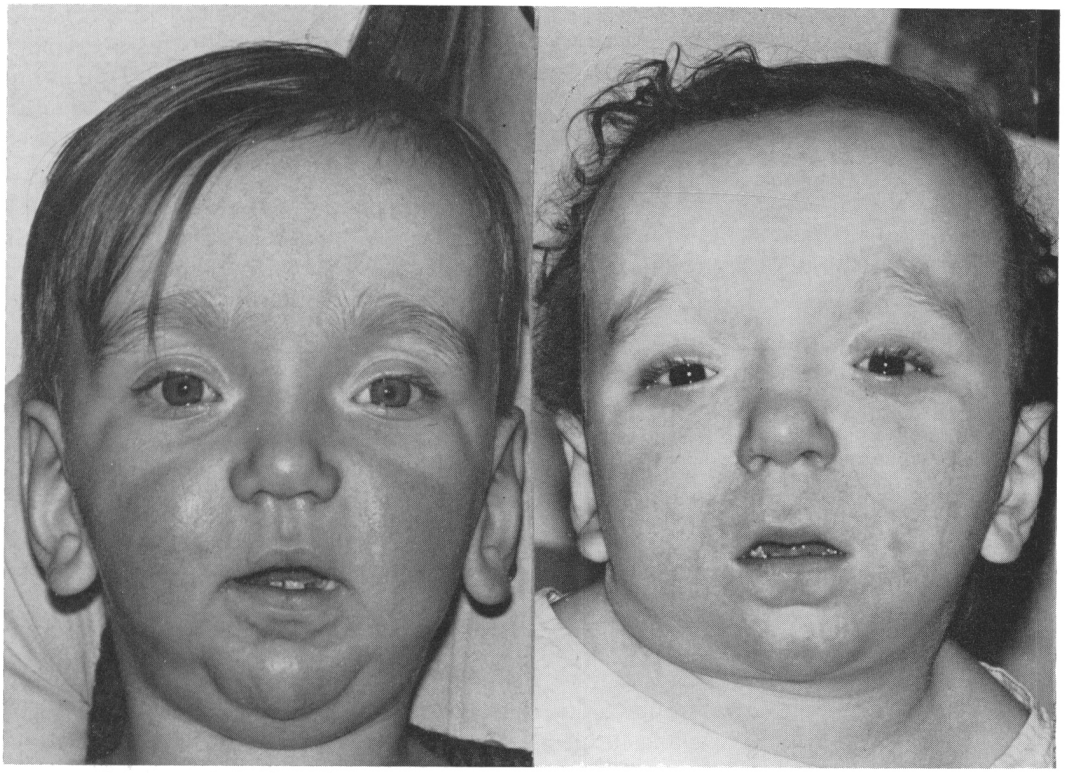

Fig. 4. An example of a recurrent-pattern syndrome in two patients. Note wide bifrontal diameter, ocular hypertelorism, large ears, long philtrum, and micrognathia. (From D. Weaver et al., J. Pediatr. 84: 547, 1974. See Fig. 5 and Table 1).

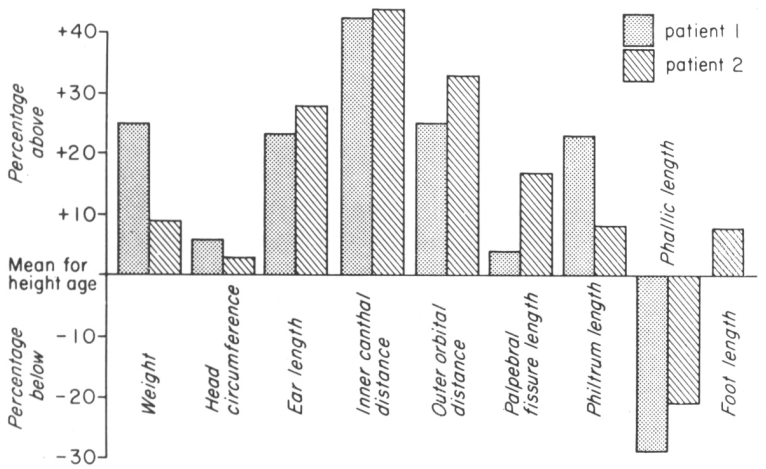

Fig. 5. An example of a recurrent-pattern syndrome in two patients. Note similarity of measurement patterns. (From D. Weaver et al., J. Pediatr. 84: 547, 1974. See Fig. 4 and Table 1).

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Table 1. *Comparison of features of two patients with recurrent-pattern syndrome* (see Figs. 4, 5)
(From D. Weaver et al., J. Pediatr. 84: 547, 1974)

	Patient 1	Patient 2
Excessive growth of prenatal onset	+++	+++
Accelerated osseous maturation	++++	++++
Performances:		
Hypertonia	++	+
Hoarse low-pitched cry	++	++
Developmental delay	?	?
Excessive appetite	++	++
Craniofacial:		
Wide bifrontal diameter	+++	+++
Flat occiput	+	+
Large ears	+++	+++
Ocular hypertelorism	++	++
Long philtrum	++	+
Relative micrognathia	+	+
Limbs:		
Hands:		
Prominent finger pads	++	++
Simian crease	—	+
Camptodactyly	++	+
Broad thumbs	++	+
Thin, deep-set nails	++	++
Feet:		
Clinodactyly, toes	+	+
Talipes equinovarus	++	—
Short fourth metatarsals	+	—
Limited early elbow and knee extension	+	+
Widened distal femurs and ulnae	++	++
Skin:		
Excessive loose skin	++	++
Inverted nipples	+	+
Thin hair	+	+
Others:		
Umbilical hernia	++	+
Inguinal hernias	++	—

+ through ++++ = present, in varying degrees of severity; — = absent; ? = uncertain.

in two or more patients suggest that the developmental pathogenesis in each case may be the same.[9] In general, the validity of the defined syndrome increases the more abnormalities there are in the condition, the rarer these abnormalities are in the general population, and the more patients that are known to have the syndrome.

[9] An identical concept for the recurrent pattern syndrome was proposed by Opitz et al. (1969) under the term *formal-genesis syndrome*. The term "formal genesis" was used by Grüneberg (1947) to refer to the "mechanism which leads to... the appearance in development of a disease" (i.e., its pathogenesis). He contrasted this with the "causal genesis" (i.e., etiology) of a disease. The term "formal genesis" has long been used in the German medical literature. However, to our knowledge, Opitz et al. (1969) coined the term "formal-genesis syndrome". We prefer not to use the term formal-genesis syndrome because it *states* that the formal genesis (developmental pathogenesis) is the same or similar in the two or more patients. While we would hope that this is true, the term is *speculative* and does not describe the actual stage in the delinea-

At the recurrent-pattern syndrome stage of delineation, the number of findings is usually expanded as the number of patients increases. However, because the etiology remains unknown at this point in time, other examples of the syndrome tend to be selected because they most closely resemble the first case. This results in an artificial homogeneity of cases, which emphasizes the most severe aspects of the syndrome. The problem of artificial homogeneity in recurrent-pattern syndromes will be explored more fully later in the text.

A known-genesis syndrome [10] *can be defined as two or more abnormalities causally related on the basis of* (*a*) *occurrence in the same family, or less conclusively, the same mode of inheritance in different families;* (*b*) *a chromosomal defect;* (*c*) *a specific defect in an enzyme or structural protein; or* (*d*) *a teratogen or environmental factor.*

B.1. The term *pedigree syndrome*, as used here, *refers to known genesis established on the basis of pedigree evidence alone; the basic defect itself remains undefined, although it is known to represent a monogenic or possibly polygenic disorder.* Although the term pedigree syndrome could be applied to an inherited translocation, an enzymatic defect, or an abnormal structural protein,[11] the term, as noted above, is restricted in its use to undefined monogenic syndromes as a stage in syndrome delineation. The Gardner syndrome and the Carpenter syndrome are examples of pedigree syndromes.

B.2. *A chromosomal syndrome* — such as trisomy 21 — is *cytogenetically defined.*

B.3. *In a biochemical-defect syndrome, the specific enzymatic defect is known in recessive syndromes* such as sulfoiduronate sulfatase deficiency in Hunter syndrome A. *The broader term, biochemical-defect syndrome*, rather than enzymatic-defect syndrome, *is used for this stage of delineation to include specific defects in structural proteins when these become known in some of the dominant disorders.* The term biochemical-defect syndrome does not include biochemical findings other than the basic defect. For example, elevation of serum pipecolic acid in the Zellweger syndrome does not make it a biochemical-defect syndrome. In its present stage of delineation, the Zellweger syndrome still remains a pedigree syndrome.

B.4. *An environmentally-induced syndrome*, such as the fetal alcohol syndrome or aminopterin syndrome, *is defined in terms of the causative teratogen or environmental factor.*

Several points should be clarified about the process of syndrome delineation. In some instances, a syndrome may be delineated in one step, thus bypassing some of the stages discussed earlier. For example, if a new chromosomal abnormality is discovered during the laboratory investigation of a patient clinically defined as having a provisionally-unique-pattern syndrome, the patient represents a known-genesis syndrome of the chromosomal type in a one-step delineation. However, the variability of the clinical expression must await the discovery of more patients. In other instances, such a large dominant pedigree with many affected individuals, a known-genesis syndrome of the pedigree type and much of its phenotypic variability can be determined in one step.

tion process. We usually know almost nothing about the pathogenesis of the condition at this point in time and commonly even after the causal genesis is known. To name a condition after what is presumed, but not known, is misleading. Furthermore, the term formal-genesis syndrome has not been well-received by clinical geneticists, and very few have adopted the term or, more importantly, made use of the concept of their writings.

[10] The term *causal-genesis syndrome* has been used by Opitz et al. (1969).

[11] Technically, the term pedigree syndrome could also be applied to a familial occurrence of a nongenetic syndrome. However, we have chosen a restricted use of the term, as discussed in the text.

It should be carefully noted that some provisionally-unique and recurrent-pattern syndromes are remarkably well-described in the older literature. Many workers today (*a*) do not have access to much of the old literature before the turn of the century, (*b*) do not have the linguistic prowess to read many languages, or (*c*) do not have time to carry out such a literature search. Thus, it sometimes happens that after a " new " syndrome becomes well-delineated, a complete description of one or more affected patients is discovered in some eighteenth- or nineteenth-century reference. We owe a great deal to the early investigators who were limited only as prisoners of history in not being able to understand pedigree analysis, chromosomal aberrations, or enzymatic defects and in not having large numbers of colleagues to communicate with regularly at national meetings, through journals, and by telephone.

Table 2 compares the syndrome-delineation terms proposed here with genetic terms in common usage. It should be carefully noted that most delineation terms are not equivalent to genetic terms in common usage — the primary reason for their proposal. Syndrome-delineation terms are hierarchical, reflecting the state of our knowledge of any given syndrome.

Table 2. *Comparison between syndrome-delineation terms and common genetic-usage terms* *

Syndrome-delineation terms	Common genetic-usage terms
Unknown-genesis syndrome	Monogenic syndrome
Provisionally-unique-pattern syndrome	→ Undefined basic defect
Recurrent-pattern syndrome	→ Enzymatic defect
	→ Structural-protein defect
Known-genesis syndrome	
Pedigree syndrome	→ Polygenic syndrome
Biochemical-defect syndrome	
Chromosomal syndrome	→ Chromosomal syndrome
Environmentally-induced syndrome	→ Environmentally-induced syndrome

* Syndrome-delineation terms are hierarchical. There are very few equivalences between syndrome-delineation terms and common genetic-usage terms. Arrows demonstrate equivalences, two of which are exact and two of which incorporate the meanings of more than one common genetic-usage term.

Syndrome delineation and the use of the delineation terms proposed should be thought of as a dynamic, flexible, and continually changing framework in which to view various syndromes. They should never be thought of as static, immutable categories, even at the higher stages of syndrome delineation. Etiologic and clinical heterogeneity is common and should be expected to occur even when not readily apparent. Probably a recurrent-pattern syndrome like the Noonan syndrome is etiologically heterogeneous. In a known-genesis syndrome of the pedigree type, heterogeneity may also be present, as in the autosomal dominant and autosomal recessive forms of the tricho-rhino-phalangeal syndrome. Even in a known-genesis syndrome of the biochemical-defect type, etiologic heterogeneity may occur, as in the hydroxylysine-deficient and procollagen peptidase-deficient forms of the Ehlers-Danlos syndrome.

Finally, we should not confuse syndrome delineation with our understanding or lack of understanding of the syndrome's pathogenesis, even at the higher stages of delineation. In a pedigree syndrome, such as the autosomal recessively inherited Meckel syndrome, we

know nothing about how the homozygous state of the Meckel gene produces such diverse features as encephalocele, polydactyly, and polycystic kidneys. We understand nothing about the pathogenesis of the trisomy-21 syndrome, although the etiology is known. How an etiologic agent, such as ethyl alcohol, produces the abnormalities found in the fetal alcohol syndrome, is still a mystery.

SPECIAL SYNDROME CATEGORIES

The following special syndrome categories will be defined and discussed separately.

(A) Weak recurrent-pattern syndrome
(A.1) Chance syndrome
(A.2) Variant additive syndrome
(A.3) Association syndrome
(B) Exceptional syndrome
(B.1) Exceptional chromosomal syndrome
(B.2) Exceptional monogenic syndrome

A. *Weak Recurrent-Pattern Syndrome*

Weak recurrent-pattern syndromes tend to have several characteristics. First, the phenotypic spectrum tends to consist of very few abnormalities, most commonly two, but occasionally more. Second, the abnormalities are weakly (although positively) correlated statistically. Third, such syndromes are usually composed of common abnormalities, although some may consist of uncommon or even rare abnormalities. Examples of weak recurrent-pattern syndromes include the binary combination of cleft palate with atrial septal defect (Shah et al. 1970) or synophrys with pilonidal cyst (Sebrechts 1961). Another example with uncommon abnormalities is the combination of hemihypertrophy and Wilms tumor.

With weak recurrent-pattern syndromes, the process of syndrome delineation usually becomes arrested. For example, new patients with the binary combination of cleft palate and atrial septal defect continually come to light. However, the phenotypic spectrum is not expanded and the etiology remains obscure.[12]

A.1. *Chance Syndrome*

A chance syndrome represents the fortuitous occurrence of two or more abnormalities in the same individual. The abnormalities are presumed to arise from different causes acting independently. The theoretical frequency with which this occurs can be calculated by summing the products of the frequencies of each possible combination of abnormalities in the general population (Cohen 1976). For example, if a total of only three abnormalities existed hypothetically in the general population with frequencies of a, b, and c, respectively, then the frequencies of specific chance syndromes in the population would be $f_1 = ab$, $f_2 = bc$, $f_3 = ac$,

[12] Even some relatively common and well-known recurrent-pattern syndromes with many highly correlated abnormalities share a similar fate. Thus, even though new examples of the de Lange syndrome, Prader-Willi syndrome, and Rubinstein-Taybi syndrome come to light almost daily, their respective etiologies remain unknown.

and $f_4 = abc$, and the total frequency with which all chance syndromes occur in the general population would be $\Sigma f = ab + bc + ac + abc$.

Chance syndromes account for only a small percentage of all multiple-abnormality syndromes. Most of them represent binary combinations of defects. Generally, the more abnormalities there are in a chance syndrome, the rarer the occurrence of that particular chance syndrome in the general population and, hence, the more likely it is to be unique. Finally, it should be carefully noted that even though we can calculate the theoretical frequencies of chance syndromes in the general population, *we cannot identify them individually as such.* An exception is the variant additive syndrome (vide infra).

A.2. *Variant Additive Syndrome*

A variant additive syndrome may be defined as several minor abnormalities and one major abnormality occurring in the same individual such that the pattern of defects in that individual is statistically abnormal compared to the general population, but biologically continuous compared to the individual's family, with the possible exception of the major abnormality.[13]

A typical example is a proband with downslanting palpebral fissures, ear pits, mandibular prognathism, clinodactyly, cubitus valgus, and ventricular septal defect. In examining the proband's relatives (Fig. 6), the father is noted to have downslanting palpebral fissures and

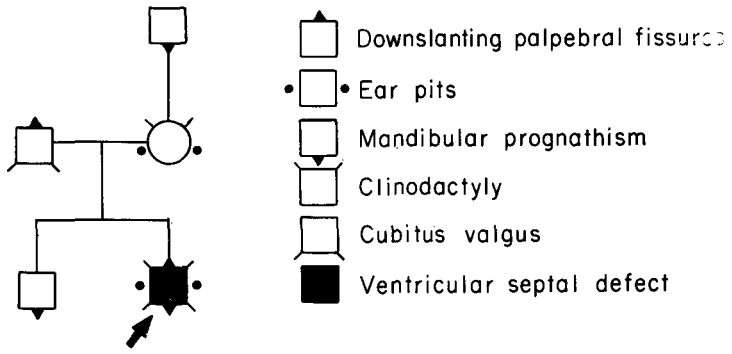

Fig. 6. An example of a variant additive syndrome. Note that all the features of the syndrome observed in the proband except ventricular septal defect are dispersed in various members of the family as minor abnormalities.

cubitus valgus, the mother is found to have ear pits and clinodactyly, and both the brother and the maternal grandfather are observed to have mandibular prognathism. Thus, all the features of the syndrome, except ventricular septal defect, are dispersed in various members of the family as minor abnormalities. They all happened to come together in the proband in addition to one major anomaly — a ventricular septal defect. Such a variant additive syndrome is usually sporadic and is not presumed to be caused by a monogenic or a chromosomal abnormality, but by a variety of different genes acting independently. Thus, a variant additive syndrome is a chance syndrome that can be identified individually in the population (see Chance Syndrome above). The probability of all these abnormalities coming together again

[13] A similar concept was introduced by Herrmann and Opitz (1974) under the term *variant familial developmental pattern.*

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in future offspring in this family is slight, although various individual anomalies or combinations of anomalies may recur. For example, of three future offspring, a first might have ear pits; a second, ventricular septal defect, clinodactyly, and downslanting palpebral fissures; a third, mandibular prognathism and cubitus valgus. The second might be interpreted as another example of the variant additive syndrome with " some of its features not expressed." Thus, a variant additive syndrome may be considered unique to an affected individual or to an affected family. In this particular family, genetic counseling should definitely include a polygenic recurrence risk for ventricular septal defect.

A.3. *Association Syndrome*

An association syndrome is a weak recurrent-pattern syndrome that occurs more commonly in the population than expected by chance. For example, the binary combination of cleft palate and atrial septal defect is known to occur in the general population more frequently than expected by chance. Thus, of the total number of cases of cleft palate and atrial septal defect in the population, some cases occur by chance and others do not. The latter are presumed to have a common cause.

The number of chance cases in the population can be estimated (see Chance Syndrome above). The total number of cases minus the estimated number of chance cases equals the number that represents association syndromes. In practice, association syndromes and chance syndromes cannot be told apart.

B.1. *Exceptional Chromosomal Syndrome*

An exceptional chromosomal syndrome is a malformation syndrome caused by an apparently unique chromosomal rearrangement, usually involving two or more breaks, which may occur sporadically or segregate within a family.[14] Since the probability of occurrence in another family is slight, the syndrome is considered unique to an affected individual or an affected family.

B.2. *Exceptional Monogenic Syndrome*

An exceptional monogenic syndrome is a pedigree- or biochemical-defect syndrome which is apparently unique to an affected family. An exceptional monogenic syndrome cannot be proven to exist absolutely. It can only be postulated to exist because a second affected family has never come to light during a " reasonable " time span despite the active interest of many clinical geneticists around the world. A possible example of an exceptional monogenic syndrome of the pedigree type is the autosomal dominant Böök syndrome consisting of premolar agenesis, hyperhidrosis, and early whitening of the hair (Böök 1950). A possible example of an exceptional monogenic syndrome of the biochemical-defect type is sulfite oxidase deficiency (Mudd et al. 1967). Obviously, a future report of affected individuals with either of these disorders would invalidate them as exceptional monogenic syndromes.

[14] A similar concept was introduced by Opitz et al. (1969) and later clarified (Herrmann and Opitz 1974) under the term *private syndrome*.

Table 3. *Population definition of a hypothetical syndrome*

Specific abnormality	Frequency of abnormality in syndrome population (% values)	Frequency of abnormality in control population (% values)
A	100	1.00
B	90	0.15
C	65	0.35
D	52	0.09
E	43	0.75
F	36	0.17
G	11	0.06
H	3	0.12
I	1	0.04
J	0.04	0.05
K	0.00004	0.001

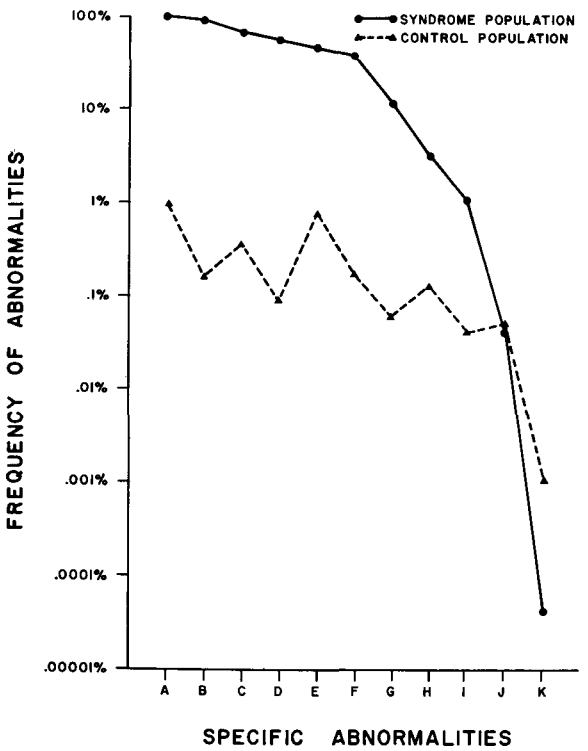

Fig. 7. Population definition of a hypothetical syndrome. Graphic representation (semilogarithmic) of Table 3 comparing the frequency of abnormalities in the syndrome population with the frequency of the same abnormalities as isolated defects in a control population. Note that abnormalities A through I all occur with greater frequency in the syndrome population than in the control population. Therefore, they are all part of the syndrome. Since abnormality K occurs considerably less frequently in the syndrome population than in the control population, its absence should be considered part of the syndrome. Finally, since abnormality J occurs with approximately the same frequency in both syndrome and control populations, its occurrence in the syndrome is probably coincidental.

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POPULATION DEFINITION OF A SYNDROME

Not all abnormalities occur with the same frequency in a given syndrome. Some are common; others are rare. The term *phenotypic spectrum* (Opitz et al. 1969) refers to the total number of abnormalities in a given syndrome and their respective frequencies in the syndrome population.

It is sometimes asked if an occasionally observed abnormality is part of a syndrome or not. Since the pathogenesis of many syndromes is obscure, there is no direct way of knowing. However, by using the population definition of a syndrome, it can be determined indirectly. Table 3 lists and Fig. 7 illustrates the phenotypic spectrum of abnormalities (A, B,...,K) of a hypothetical syndrome together with their frequencies in the syndrome population and in a control population. If a given abnormality occurs with greater frequency in the syndrome population than as an isolated abnormality in the control population, it should be considered part of the syndrome. Thus, by comparing the frequencies in Table 3 and Fig. 7, abnormalities A through H are obviously part of the syndrome. Even abnormality I (1% compared with 0.04%) should be considered part of the syndrome. This principle commits us to statements such as "cleft palate is part of the Down syndrome" because it occurs with higher frequency than as an isolated defect in the control population.

Abnormality J occurs with approximately the same frequency in both syndrome and control populations (0.04% compared with 0.05%). Thus, it should not be considered part of the syndrome.[15]

Note that abnormality K occurs with significantly lower frequency than as an isolated defect in the control population (0.00004% compared with 0.001%). Conspicuous absence of an abnormality should be considered part of the syndrome. A possible example is osteogenesis imperfecta, which has been suggested to be a cancer-resistant genotype (Lynch et al. 1966). Various malignant neoplasms apparently occur at a lower rate in patients with this disorder than they do in normal first-degree relatives or in the general population. A possible exception may be osteosarcoma, which may occur at a slightly higher rate (Klenerman and Oskenden 1967, Miller 1969).

Thus far, we have discussed a control population without specifying its nature. If a syndrome is ascertained independently of its phenotype, which is possible with a known-genesis syndrome of the chromosomal, biochemical-defect or environmentally-induced type, an unbiased estimate of its phenotypic spectrum can be obtained. The ideal control population is one composed of unaffected first-degree relatives. However, it may not be practical to use first-degree relative populations. If the syndrome is rare, which is frequently the case, large syndrome and control populations may not be available. In such instances, it is difficult to establish low-frequency abnormalities as part of the syndrome with certainty since large syndrome and control populations are required to do this.

If ascertained independently of the phenotype, the syndrome can probably be compared directly with the frequencies of isolated abnormalities in the general population. One obvious advantage is that frequencies of various isolated abnormalities are readily available in the literature. Thus, a rough comparison can be made without extensive calculations. However,

[15] Except in the probably rare, hypothetical circumstance in which the biological makeup of the syndrome suppresses the frequency of abnormality J either partially or completely through one developmental pathway, but allows for its expression through an alternate pathway with the same frequency as the suppression frequency.

it should be recognized that the general population is not the same as a normal first-degree relative population. Thus, the comparison should be made with caution, depending upon the " appropriateness " of the general population utilized.

Estimating the frequencies of various abnormalities from probands with a known-genesis syndrome of the pedigree type truncates the syndrome towards the severe end of the phenotypic spectrum (Fig. 8). The ascertainment bias introduced by using probands probably cannot be balanced by including mildly affected patients born before the proband. Since there is a greater chance of ascertaining a family with several severely affected members than there is of ascertaining a single case, there is a bias in favor of severely affected patients. Adding in the mildly affected patients that come to light in all sibships in the study probably leads to a bimodal frequency distribution of abnormalities per patient, reflecting the mild and severe ends of the phenotypic spectrum (Fig. 8). An unbiased estimate of the phenotypic

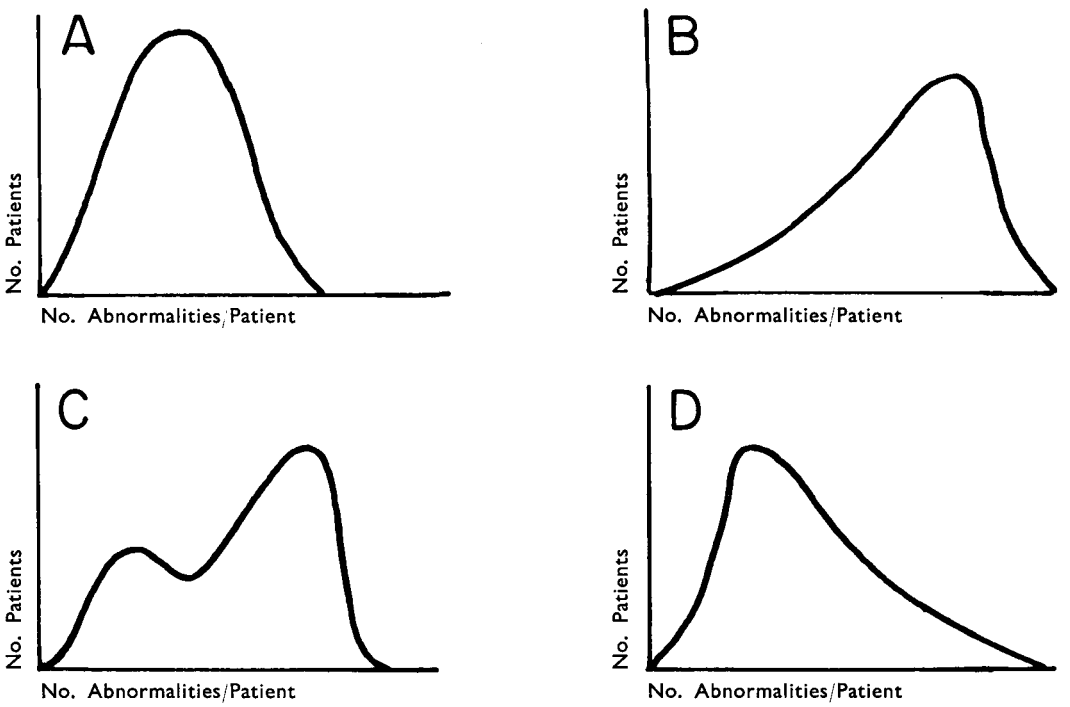

Fig. 8. The phenotypic spectrum of a syndrome.
(A) The normal phenotypic spectrum that occurs when the syndrome population is ascertained independently of the phenotype, as is possible with a chromosomal syndrome, a biochemical-defect syndrome, or an environmentally-induced syndrome. This phenotypic spectrum also occurs when the ascertainment bias has been corrected in a pedigree syndrome by including only affected sibs born after the proband and excluding the proband.
(B) Syndrome population truncated towards the severe end of the phenotypic spectrum. Such artificial homogeneity occurs when a syndrome population is ascertained by phenotypic features, as in a recurrent-pattern syndrome.
(C) Syndrome population with bimodal distribution emphasizing both severe and mild ends of the phenotypic spectrum. Such a distribution composed of probands plus previously unrecognized, mildly affected sibs who were born before the proband and actively searched for.
(D) Syndrome population truncated towards the mild end of the phenotypic spectrum.

spectrum in a pedigree syndrome can be obtained by including only those affected sibs born after the proband (Fig. 8). To avoid ascertainment bias, probands are excluded. The more families there are in the study, the greater the chance of balancing intra- and intersibship variability (Opitz et al. 1969).

As we indicated earlier, in a recurrent-pattern syndrome, there is an artificial homogeneity of cases which emphasizes the most severe aspects of the syndrome. The etiology is unknown and the disorder cannot be ascertained independently of the phenotype. Nor can ascertainment bias be corrected for as in a pedigree syndrome because the affected individuals in the syndrome sample are unrelated. Thus, the population definition of a syndrome is more complex in a recurrent-pattern syndrome.

To determine the frequency at which a given abnormality probably occurs by chance in recurrent-pattern syndrome, it is necessary to know the frequency of the syndrome in the general population [16] and the frequency of the abnormality in question as an isolated trait in the general population. The probability that the abnormality occurs in the syndrome by chance is equal to the product of the two separate frequencies. Consider the recurrent pattern syndrome shown in Table 4. For comparative purposes, the frequencies of abnormalities A

Table 4. *Population definition of a recurrent pattern syndrome* *

Specific abnormality	Frequency of abnormality in general population	Frequency of abnormality in general population × frequency of syndrome in general population (2×10^{-4})	Frequency of abnormality in syndrome population
A	10×10^{-3}	20×10^{-7}	1×10^{0}
B	1.5×10^{-3}	3×10^{-7}	9×10^{-1}
C	3.5×10^{-3}	7×10^{-7}	6.5×10^{-1}
D	0.9×10^{-3}	1.8×10^{-7}	5.2×10^{-1}
E	7.5×10^{-3}	15×10^{-7}	4.3×10^{-1}
F	1.7×10^{-3}	3.4×10^{-7}	3.6×10^{-1}
G	0.6×10^{-3}	1.2×10^{-7}	1.1×10^{-1}
H	1.2×10^{-3}	2.4×10^{-7}	0.3×10^{-1}
I	0.4×10^{-3}	0.8×10^{-7}	0.1×10^{-1}
J	0.5×10^{-3}	1×10^{-7}	0.4×10^{-3}
K	0.1×10^{-4}	0.2×10^{-8}	0.4×10^{-6}

* Column four should be compared to column three.

through K in the syndrome population and the frequencies of abnormalities A through K as isolated traits in the general population are the same as those shown in Table 3. If a recurrent-pattern syndrome has a prevalence of one in 5000 (2×10^{-4}) in the general population and an abnormality in question, say B, occurs as an isolated trait in 0.05% (1.5×10^{-3}) of the general population, then the probability that the abnormality occurs in the syndrome by chance equals approximately 3×10^{-7}. The values for which various abnormalities occur in the syndrome population by chance are listed in the third column of Table 4. By comparing these values to the actual frequencies with which abnormalities occur in the syndrome popu-

[16] This can be extremely difficult, if not impossible, to determine.

lation (column 4), it should be noted that all abnormalities, including J and K, occur with higher frequency in the syndrome population than expected on the basis of chance.

As we have indicated, there are many obstacles to determining the phenotypic spectrum for syndromes at different stages of delineation. Thus, we should be wary of exact percentages given for various abnormalities in most syndrome-review articles and textbooks. Percentages can be very misleading in recurrent-pattern syndromes. Even in known-genesis syndromes of the pedigree, chromosomal, biochemical-defect, or environmentally-induced types, no attempt is made to correct for ascertainment bias in the phenotypic frequencies given in most syndrome-review articles. Studies of the phenotypic spectrum are especially hampered by our incomplete knowledge of low-frequency abnormalities in various syndromes. This is regrettable since low-frequency abnormalities may be the most susceptible to fluctuation across populations, i.e., dramatic changes in the genetic background may possibly change low-frequency abnormalities while leaving high-frequency abnormalities undisturbed. For example, in a karyotyped study of a Chinese Down-syndrome population, 7% of all patients were noted to have syndactyly *of the hands*, an extremely rare finding in a white Down-syndrome population (Emanuel et al. 1968). The phenotypic spectrum of various syndromes across populations deserves further study.

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RIASSUNTO

Sulla Natura della Delineazione delle Sindromi

Forse la metà di tutti i pazienti con anomalie multiple presenta sindromi note e riconosciute, mentre l'altra metà presenta entità sconosciute che richiedono di essere ulteriormente delineate. L'importanza della delineazione delle sindromi è notevolissima. Con la delineazione di una sindrome, divengono noti il suo spettro fenotipico, la sua storia naturale, ed il suo rischio in termini di frequenza, il che consente di migliorare il trattamento e la consulenza eugenica.
Il processo della delineazione delle sindromi viene discusso riferendosi alle sindromi con genesi sconosciuta dei tipi ' provvisoriamente unico ' e ' ricorrente ', ed alle sindromi con genesi nota dei tipi ' genealogico ', ' cromosomico ', ' da difetto biochimico ', ' di origine ambientale '. Vengono definite diverse categorie di sindromi speciali e viene infine elaborata una definizione popolazionistica di sindrome.

RÉSUMÉ

Sur la Nature de la Délinéation des Syndromes

Peut-être la moitié des patients atteints d'anomalies multiples présente des syndromes reconnus, alors que l'autre moitié présente des entités inconnues pour lesquelles une délinéation ultérieure est nécessaire. La délinéation des syndromes est très importante. Une fois un syndrome délinéé, son spectrum phénotypique, son histoire naturelle et son risque d'affection deviennent connus, ce qui améliore le traitement des patients et la consultation familiale.
Le processus de délinéation des syndromes est discuté par rapport aux syndromes à genèse inconnue (types ' provisoirement unique ' et ' récurrent ') et à genèse connue (types ' généalogique ', ' chromosomial ', ' à défaut biochimique ', ' d'origine environnementale '). Différentes catégories spéciales de syndromes sont définies et une définition de syndrome par rapport à la population est finalement élaborée.

ZUSAMMENFASSUNG

Ueber die Abgrenzung von Syndromen

Vielleicht nur die Hälfte aller Patienten mit multiplen Anomalien leiden an bekannten und bereits anerkannten Syndromen. Die andere Hälfte leidet an noch unbekannten Krankheitsbildern, die noch genauer umrissen werden müssen. Die genaue Abgrenzung der Syndrome ist von grösster Wichtigkeit, denn nur dadurch kann man ihr phänotypisches Spektrum, ihre Naturgeschichte sowie das Risiko erfassen, das ihr mehr oder minder häufiges Vorkommen in sich birgt, um Behandlung und eugenische Beratung dementsprechend zu verbessern. Es wird daher erörtert, wie sich die Syndrome abgrenzen lassen. Syndrome unbekannten Ursprungs kann man in « vorläufig » und « wiederholt auftretende » einteilen. Bei Syndromen bekannten Ursprungs lassen sich hingegen « genealogische », « chromosomale » sowie « durch biologische Defekte bedingte » und « umweltsbedingte » Syndrome unterscheiden. Es werden noch verschiedene Kategorien von Sondersyndromen beschrieben und schliesslich eine auf die Bevölkerung bezogene Definition des Begriffs Syndrom ausgearbeitet.

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