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Terminology of Genetic Syndromes

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The use of eponyms is unquestionably overdone and, in the opinion of all authorities, should be avoided whereever possible. Nevertheless, the names of certain great men in medicine should not be forgotten by younger generations and should be preserved for posterity. Parkinson's disease, Babinski's sign, Banti's syndrome, Mikulicz's disease and similar eponyms should stay and remind of the merits of such men. (cf. BAUER, J.: Logic and Language in Medical Writing. Science, 1953. 117, 40). The last brilliant voice against the abuse and particularly the unjustified use of eponyms was that of Richard Asher (1). He pointed out that the well known Pel-Ebstein's type of Hodgkin's disease, for instance, turned out to be a misnomer. Reading the original papers of both Pel and Ebstein convinced Asher that their patients had been suffering from chronic relapsing fever, probably brucellosis, nothing suggesting a not even mentioned Hodgkin's disease. Yet even Asher himself, the originator of *Muenchhausen-syrdrome*, can not be acquitted completely of a similar sin. Muenchhausen did neither describe the syndrome nor did he present it as its victim. Baron von Muenchhausen was a liar, a story teller about his impossible adventures. The persons with Asher's Muenchhausen-syndrome are not braggarts and do not tell impossible stories. They are psychopaths not with ,, pseudologia phantastica " but with a variety of what I have calles *surgicophilia* or *iatrophilia* (2). They seek for attention and sympathetic care in a hospital environment, the only place and the only people where they may find what they are craving for but missing.

No field of medicine is overflowed more with eponyms than that of genetically determined clinical syndromes, and such eponyms are not always historically correct.

Marfan's syndrome is a classical misnomer of a hereditary complex of different abnormalities. What Marfan, the French pediatrician, described in 1896 (3) was a 5 ½ year old girl with various skeletal deformities, contracture of the knee joint due to retraction of tendons, spider-like long fingers and toes, and retarded mental development. Eyes and heart were normal. He spoke of " pattes d'araignées " and coined the term " arachnodactyly " or " dolichostenomelia ". Not before 1914 (4) the occasional combination of arachnodactyly with tremulousness of the ocular lens (subluxation of the lens, iridodonesis) has been reported which later became known

as Marfan's syndrome. In addition, numerous developmental anomalies were found in persons with this syndrome or with arachnodactyly alone: persisting pupillary membrane, high grade myopia, congenital hydrophthalmos, color blindness, congenital cataract, coloboma, microcornea, strabismus, funnel chest, congenital dislocation of the hip, arched or cleft palate, laxity of ligaments, spina bifida, winging scapula, malformation of lungs or teeth, dystopic or polycystic kidneys and particularly various congenital heart diseases.

Van Buchem (5) wrote a paper entitled " Arachnodactyly Heart " and described 2 brothers and their mother with cardiomegaly due to hypertrophy and fibrosis. Best known and most frequent, however, is a dissecting aneurysm of the aorta. In one report it was the cause of death of a mother and son. Dissecting aneurysm develops on the anatomical basis of Erdheim's cystic medionecrosis. It occurs with particular frequancy but by no means only in persons with arachnodactyly. Marfan had no knowledge of all these common associations of arachnodactyly with other constitutional aberrations, he actually had not described any syndrome at all; if he were alive today he would be amazed to hear arachnodactyly being called his „ syndrome " and dissecting aneurysm without arachnodactyly its forme fruste.

Golden and Lakin (6) reported on such „ forme fruste in Marfan's syndrome ". A 10 year old boy had arachnodactyly with various skeletal deformities including pectus excavatum, webbing of the neck (pterygium colli) and a heart lesion. His 7 year old brother apparently had no arachnodactyly but pectus excavatum, scoliosis, pterygium colli, an interatrial septum defect and an arcus juvenilus (*sic!*), whatever that is. A half-sister had only pectus excavatum and slight scoliosis, and the 50 year old father only pectus excavatum and " a possible defect of the interatrial septum as part of a hereditary connective-tissue disorder ". The listing of " coloboma of the lens " (*sic!*) among the signs of Marfan's syndrome is obviously a lapsus calami as is the " and " separating arachnodactyly from its synonym dolichostenomelia.

The etiology, however, of all these signs of abnormal development associated with arachnodactyly and commonly designated by the misnomer Marfan's syndrome is not unexplained as has been declared in an editorial of the Brit. Med. J. (1958, Oct. 11. 903) or by Roark (7) who identifies Marfan's syndrome with arachnodactyly which is not a syndrome but a sign. It is in fact a more or less wide spread abnormality of one or more genes.

An inherited defect of mesodermal tissues, connective tissue, elastic fibers (8) has been advocated but microcornea, color blindness, imbecility and some other abnormalities do not fit into this concept. The idea of genetic abnormality of connective tissue is not new although the term " diathèse fibreuse " (Hanot, Huchard a. o.) and " Bindegewebsdiathese " of German authors had been applied to explain quite different clinical syndromes at a time when scientific genetics did not exist (9). Sjoerdsma et al. (10) found in Marfan's syndrome increased excretion of hydroxyproline which is almost entirely present in collagen. Yet, to my knowledge, they did not indicate what justified the term Marfan's syndrome in their cases. What

is termed " collagen disease " obviously has nothing to do with Marfan's syndrome.

Genetic syndromes — literally running together — are defined as typical associations of pathogenetically independent abnormal clinical signs that are associated with a frequency significantly exceeding a chance combination, and are caused by a hereditary factor, either one pleiotropic gene or linkage of genes. As to the many various genetic abnormalities found in persons with Marfan's arachnodactyly only its combination with subluxation of the lens and cystic medionecrosis of the aorta fulfills this criterium. Each of the three manifestations may be observed alone without the others, their relatively frequent combination, however, justifies the term " syndrome ". Other signs of faulty development are only trimmings, not specifically attached to this syndrome and equally frequent in combination with other genetic syndromes or occurring isolated as familial traits.

A mild form of arachnodactyly, without any abnormalities is not uncommon especially in female Negroes and can be seen on Boticelli's paintings („ Madonnenfinger ") as a beautiful variety of human physique. Congenital heart diseases occur much more often as single somatic defects or accompany other different genetic syndromes. Pectus excavatum is a common isolated familial trait. In the family reported by Golden and Lakin it was present in 4 members, arachnodactyly only in one. The same can be said about the various malformations listed previously as recorded in association with arachnodactyly.

We meet with a similar situation in other types of coupled genetic defects. The association of obesity, genital hypoplasia, retinitis pigmentosa, mental deficiency, polydactyly sometimes with syndactyly, and deformity of the skull is rightfully known as *Bardet-Biedl syndrome* notwithstanding the fact that not all of its manifestations may be present in all cases and may be dissociated in members of the same family. Our knowledge about the action of genes explains this phenomenon satisfactorily. This syndrome also has been seen in combination with other malformations such as excessive genua valga, atresis ani a. o. Each of all these genetic defects may occur as a single familial trait more often than as part of the syndrome.

Turner's syndrome, according to his describer (11) consists of genital dysplasia, stunted growth, webbing of the neck (pterygium colli) and cubitus valgus. Among 55 cases of ovarian dysplasia Haddad and Wilkins (12) found short stature in all, webbing of the neck in 28 and cubitus valgus in 34. A shield-like chest was present in 46, overweight in 40, hypoplastic nails in 27, and pigmented moles in 20 cases. As a matter of fact, 29 different other constitutional aberrations were listed in some of the patients including epicanthal folds (in 18), low set ears (in 14), cutis laxa (in 10), keloid formation (in 10), congenital heart diseases (in 13), mental retardation (in 8), laxity of joints (in 8), deafness (in 3) and retinitis pigmentosa (in 1).

Epicanthal folds are one of the most characteristic diagnostic signs of *mongolism.* Of 200 cases of mental deficiency studied by Berg and Kirman 46 have been found to be of the mongoloid variety (13). " The more one studies these persons the less one is able to find anything normal about them " (Bleyer) (14). Cutis laxa, friability of the skin and laxity of joints characterize *Ehlers-Danlos syndrome.* Keloid formation

is a constitutional variant in the Caucasian race, it is a racial characteristic in Negroes. Deafness associated with brittle bones (fragilitas ossium) and blue sclerae is known as *Eddowes-van der Hoeve's syndrome.* This syndrome like Marfan's syndrome also had been interpreted as result of a genetic systemic defect of mesenchymal tissue. It was shown that such a concept is incompatible with the facts. (15) Low set ears accompany *hypertelorism* which has been reported in association with idiocy and skeletal deformities. In other families hypertelorism was found associated with polydactyly and other genetic defects (16). Various deformities of bones and joints in combination with imbecility, deafness, corneal cloudiness and hepatosplenomegaly due to an inborn abnormal metabolism of polysaccharides and mucopolysaccharides belong to the *syndrome of Hurler* (dysostosis multiplex, gargoylism) and the closely related *Morquio's disease* (without corneal cloudiness and mental defect). There are syndromes of hereditary arthrodysplasia with dystrophy of the nails (17), of hereditary chondroectodermal dysplasia (18) or of hereditary ectodermal dysplasia associated with primary hypogonadism (19) and accompanied with a host of other constitutional defects. Retinal degeneration, obesity, nerve deafness and diabetes in 3 members of a Swedish family have been reported recently as " a new genetic syndrome " (20).

A number of genetic syndromes has been attributed by Kristine Bonnevie in 1932 and later by O. Ullrich to the persistence of blebs of cerebrospinal fluid beneath the epidermis which normally escapes in the mouse embryo through a transitory opening in the roof of the primitive fourth ventricle, the foramen anterius, and disappears by absorption. If it is not absorbed as it should be, the persistent blebs may interfere with various developmental processes. Ullrich himself warned against boundless extension of this theory upon human genetic pathology (21).

Whatever syndrome we study, practically always we find more or less numerous unrelated genetic defects in their company. Some of them are part of another syndrome of their own, usually, however, they occur merely as trimmings of other syndromes in various distribution and frequency. Many of those genetic defects were well known to clinicians of older times as *degenerative stigmas.* In 1917 I applied this term to define unusual accumulation of such constitutional aberrations as *Status degenerativus* (9). This was meant to designate a deviation from the average type of the genus " homo ", a degeneration. The term status degenerativus has a biologic, not a pathologic-anatomic significance. Multiple genetic defects in various combinations are a deviation from that average genetic type in man which represents the best adjustment to his environment so far achieved by biologic selection. Marked deviations from this state involve, as a rule, diminished adjustment, lower resistance, greater morbidity, and often predisposition to unusual disease processes emerging from the abnormal or defective genes. Genetic syndromes are only more or less typical varieties of status degenerativus, each having its particular familial stamp.

Because the term status degenerativus has given rise to frequent misunderstanding

in German literature I used later the term *Polygenopathy* (18) which comprises also what has been called „ polydystrophy " in Great Britain (22). Many signs of deviation from a normal individual constitution occur without attachment to a typical syndrome, single or in various combinations. Some are apparent in the habitus, others are detected only on physical examination, by laboratory tests or at autopsy. The clinical importance of recognizing an accumulation of degenerative stigmata (that is, status degenerativus) lies in the fact that such individuals are poor „ biological risks " because of the generally diminished physical and mental adjustment to the environment. Status degenerativus usually is not in itself a disease, though certain single mutations may interfere with bodily functions. Only a nonspecific morbid predisposition may be inferred from the presence of multiple genetic aberrations.

For my audience of students and physicians who prefer a visual image of something concrete and tangible to abstract thinking I spoke usually of *a mess in the chromosomes* (23). This metaphorical expression now has become a reality after the brilliant discovery of British biologists under the leadership of E. C. Ford. What has largely been ignored in the past by clinicians may attract their attention in the future since they have been given a tangible morphological in addition to a biochemical basis to think about.

We are entering a new era of human genetics with difficult problems to solve in the future. How does an extra-chromosome (autosome in mongolism, X-chromosome in Klinefelter's syndrome or in a „ super-female ") or a deficient Y-chromosome in Turner's syndrome bring about all these clinical pictures of a genopathy? It will take a long time to correlate the new morphological facts with the biochemical control of enzymatic processes by genes.

Conclusions

To comply with the tendency to eliminate unjustified or dispensable eponyms without jeopardizing the necessary distinction of different groupings of genetically determined abnormal manifestations within the large frame of polygenopathies the following terminology is suggested:

Arachnodactyly syndrome (instead of Marfan's syndrome)
Ovarian dysplasia syndrome (instead of Turner's syndrome)
Fragilitas ossium syndrome (instead of Eddowes-van der Hoeve's syndrome)
Dysostosis multiplex (gargoylism) syndrome (instead of Hurler's syndrome)
Laxity of skin and joints syndrome (instead of Ehlers-Danlos syndrome)
Obesity-Polydactyly syndrome (instead of Bardet-Biedl syndrome)

Each of these leading manifestations of the listed syndromes may also occur single, not as part of these syndromes or as incidental combination with various other genetic syndromes. In those listed above, however, it is the indispensable essential center of a variety of more or less typical combinations of genetic abnormalities which justify the term „ syndrome " and the proposed terminology.

Summary

Genetically determined abnormalities of structure or function occur either single or in various combinations. As genetic syndromes should be designated only those combinations that are typical, that is, significantly more frequent than would be expected from pure chance association. Some genetic defects are part of a syndrome or they only accompany other syndromes as irregular trimmings in various distribution and frequency. The accumulation of such " degenerative stigmas " as they were known to clinicians of an older generation had been called " status degenerativus " or " polygenopathy " and attributed to a " mess in the chromosomes " by the author long before this concept has been substantiated by the newest discoveries of British investigators. The biologic significance of such polygenopathies as to adaptation, resistance and general viability of their carriers has been stressed and a more satisfactory terminology suggested.

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RIASSUNTO

Le anormalità strutturali o funzionali determinate geneticamente si verificano singolarmente o in combinazioni diverse. Bisognerebbe designare come sindromi genetiche soltanto quelle combinazioni che sono tipiche, vale a dire significativamente più frequenti di quanto ci si potrebbe attendere da una pura associazione fortuita. Alcuni difetti genetici sono parte di una sindrome, oppure accompagnano solamente altre sindromi come accessori irregolari con varie distribuzioni e frequenze. L'accumulazione di tali « segni degenerativi », così come nota ai clinici di una generazione precedente, era stata chiamata « status degenerativus » o « poligenopatia » ed attribuita ad un « disordine nei cromosomi » dall'autore molto prima che questo concetto fosse reso valido dalle ultimissime scoperte dei ricercatori inglesi. E stato sottolineato il significato biologico di tali poligenopatie riguardo l'adattamento, la resistenza e la viabilità generale dei loro portatori, ed è stata suggerita una terminologia più soddisfacente.

RÉSUMÉ

Les abnormalités structurales ou fonctionnelles déterminées génétiquement se vérifient seules ou en combinations diverses. Il faudrait désigner comme syndromes génétiques rien que les combinations typiques, c'est-à-dire significativement plus fréquentes de ce que l'on pourrait expecter dans le cas d'une association accidentelle. Certains défauts génétiques font partie d'un syndrome, ou bien ils sont irrégulièrement associés à d'autres syndromes avec de diverses distributions et fréquences. L'accumulation de ces « signes dégénératifs » — ainsi qu'elle était connue aux cliniciens d'une génération plus ancienne — avait été appelée « status degenerativus » ou « polygénopathie » et avait été attribuée par l'Auteur à un « désordre des chromosomes » bien avant que cela fût prouvé par les dernières découvertes des rechercheurs anglais. L'on a souligné la valeur biologique de ces polygénopathies en ce qui concerne l'adaptation, la résistance et la viabilité générale de leurs conducteurs, et l'on a suggéré une terminologie plus appropriée.

ZUSAMMENFASSUNG

Durch Gene bedingte Abweichungen der Struktur oder Funktion kommen isoliert oder in verschiedensten Kombinationen vor. Als « genetische Syndrome » sollten nur solche Kombinationen bezeichnet werden, die typisch sind, d. h. entschieden haeufiger Vorkommen als ihr zufaelliges Zusammentreffen zu erwarten waere. Manche gen-bedingte Defekte sind obligate Teilsymptome von Syndromen oder sie sind unregelmaessige und nur gelegentliche Begleitsymptome anderer Syndrome. Im aelteren medizinischen Schrifttum wurden sie als « degenerative Stigmen » bezeichnet, ihre Haeufung in einem Individuum nannte Verf. « Status degenerativus » oder « Polygenopathie » und fuehrte sie auf eine « Unordnung im Chromosomensystem » zurueck, lange bevor eine solche « Unordnung » auch wirklich im Mikroskop gefunden werden konnte. Die biologische Bedeutung dieses Zustandes mit Ruecksicht auf Adaptationsfaehigkeit, Resistenz und allgemeine Lebensfaehigkeit des betroffenen Individuums wird hervorgehoben und eine befriedigendere Terminologie einzelner gen-bedingter Syndrome vorgeschlagen.