Turner's Syndrome and Status Bonnevie-Ullrich

A Synthesis of Animal Phenogenetics and Clinical Observations on a Typical Complex of Developmental Anomalies

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BREEDING experiments and systematic embryological studies of developmental processes are not feasible in human genetics. Hence, human physiological genetics must be based in large part upon principles which can be learned from experimental genetics. On the general applicability of basic genetic laws there is no longer a question. But, just as the mechanism of simple and complex Mendelian transmission can be verified in man in full detail, it is also becoming increasingly evident that there is a parallelism in the *modus operandi* of certain genes in both man and animal. Since certain key genes undoubtedly play identical, or at least very similar, roles in the organizational plans of various higher organisms, it is understandable that the mutations of these genes should likewise have followed similar pathways. Even peristatic (i.e., intrauterine environmental) factors can exert themselves in embryogenesis in a manner simulating the action of mutant genes. Therefore, in developmental pathology, as in developmental physiology, a striking similarity is again apparent between man and higher animals. Our knowledge of homologous hereditary variations showing a similar genetic basis and developmental course in various mammalian species and genera is steadily growing. Thus comparative phenogenetics opens up a broad field of investigation for human biology and genetics.

Especially suited for studies of this kind are the various abnormalities of general body form. To be sure, we need to forewarn ourselves against the dangers of inferring homologous genetic events for single characteristics. For we have learned from general genetics that phenotypically very similar traits can not only be due to different genes, but can also result from entirely different epigenetic events. However, the probability of drawing erroneous analogies is somewhat reduced in the case of complex characteristics. And, if a key to the understanding of apparently disconnected multiple anomalies can be acquired from observations of experimental animals, it is entirely appropriate to transfer knowledge gained in this way to an analysis of the phenogenesis of human anomaly-complexes.

Among the more highly organized species, man is the best studied with respect to teratology. A gigantic store of observation is available on human multiple anomalies or "syndromes", which morphologically can be analyzed in

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minute detail. Their formal development, however, can at best be retraced into fetal life; events falling within the embryonic period can be reconstructed only in very limited measure through systematic investigation. It is here that the teachings of comparative pathological genetics can serve as a stepping stone, since it is precisely in embryonic development that the various mammalian species show the most far-reaching analogies. Whenever it is thus possible to find in the phenogenetic processes of an animal a connection with a human syndrome, it is not essential for its extension to human genetics that there be found an exact morphologic correspondence of the end products. Even in the case of completely homologous developmental processes one may expect differences in the general plan of organization to produce certain deviations in the final mode of expression. Thus the desired synthesis demands to a considerable degree an inquiry into the phenogenetic mechanism starting from both the initial and the final stages of the process.

In the following pages a typical complex of anomalies, *Status Bonnevie-Ullrich* (St.B.U.), will serve to illustrate the various possibilities of interpretation that are afforded by a comparative analysis of developmental mechanics in the animal and clinical observations on man.

THE BAGG-LITTLE MOUSE MUTATION, "MYELENCEPHALIC BLEBS"

In what proved to be a trail-blazing discovery in the field of mammalian phenogenetics, Kristine Bonnevie (1932, 1934) was enabled by a discerning combination of genetic experiments and embryological analysis to reach a flawless clarification of the formative events underlying various multiple anomalies in an abnormal strain of the house mouse. The mutation analyzed by her was one recovered by Bagg and Little (1924) from a race of inbred, x-rayed mice. It proved to be a monogenic recessive abnormality manifesting itself in the form of very diverse *malformations of the head and extremities.* The eye defects consisted principally in a narrowing of the palpebral fissures, sometimes associated with a reduction in the size of the globe (microphthalmia) and a twisting of the snout to the same side (fig. 4). Also the ears were variously deformed;

FIGS. 1–5. Abnormalities in embryos and adults of the "myelencephalic bleb" mutation in the house mouse (Bagg-Little).

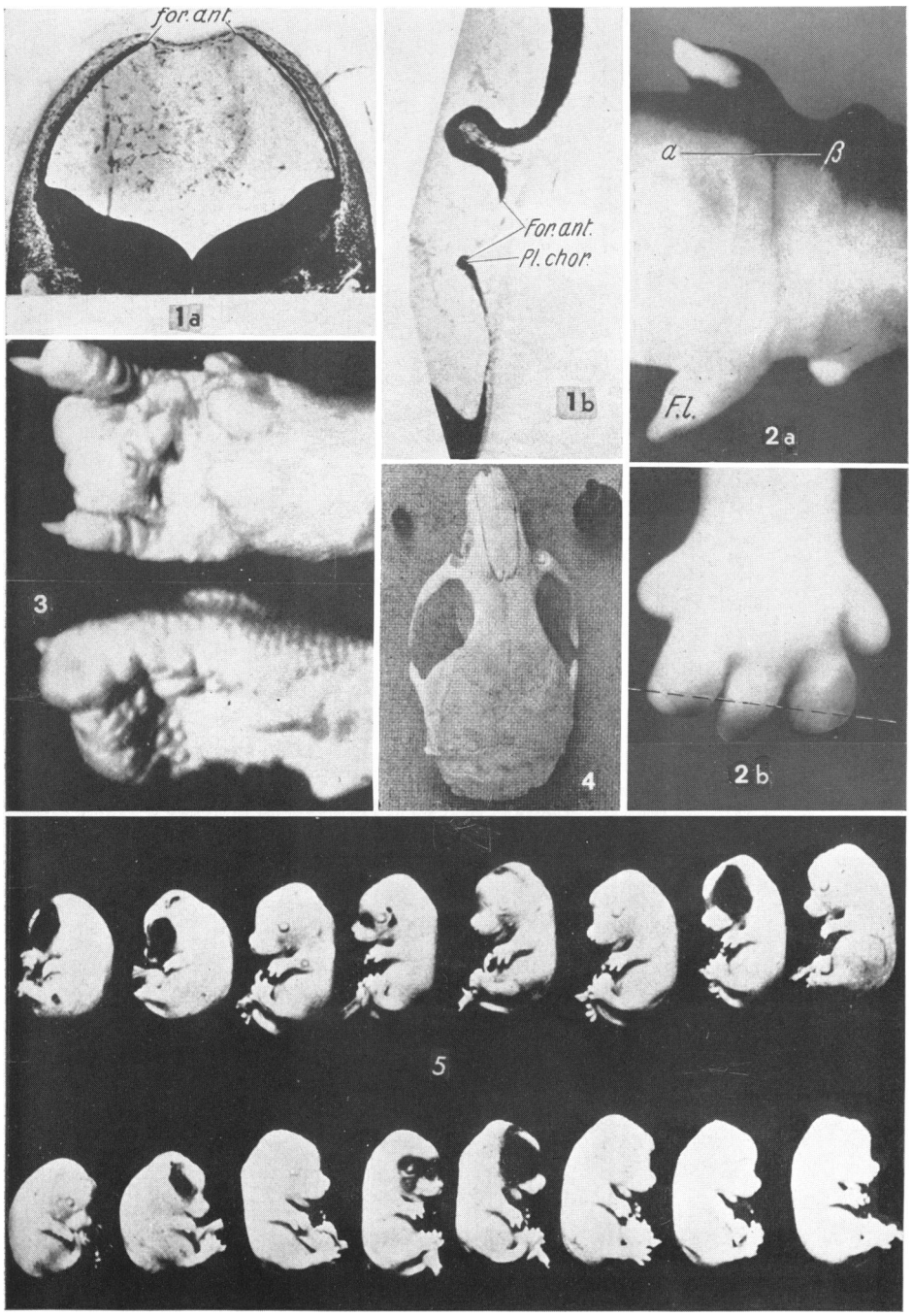
FIG. 1. *a.* Cross-section; *b.* Sagittal section through the myelencephalon in the 7 mm. embryo, showing *foramen anterius* (for. ant.). After Bonnevie, 1934.

FIG. 2. *a.* Primary blebs of the neck and shoulder region in a 10 mm. embryo; *b.* Blebs of the hind foot. After Bonnevie, 1934.

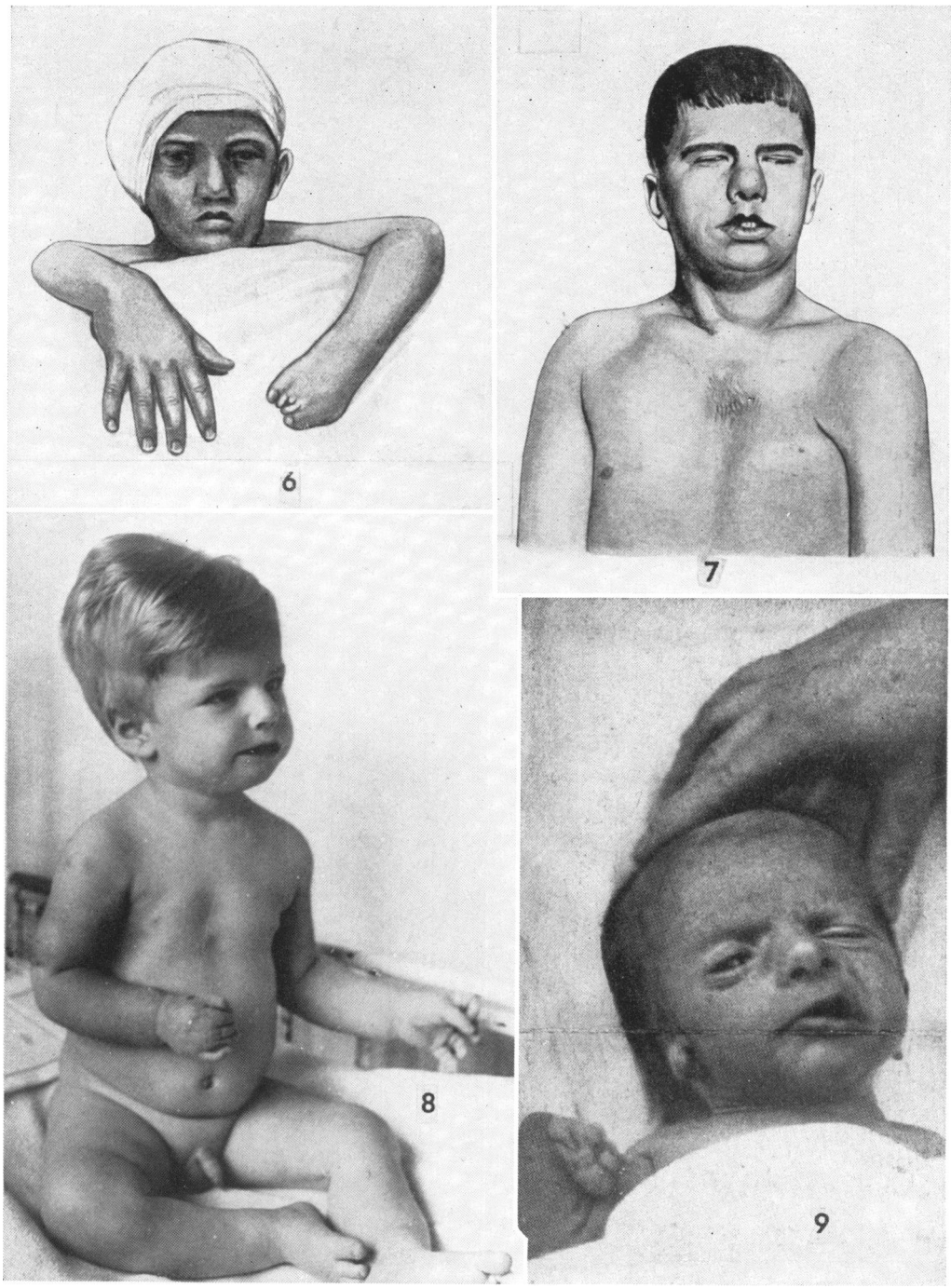
FIG. 3. Severe foot deformities in Bagg-Little mice. After Bonnevie, 1934. (Compare with figs. 6, 8 and 9.)

FIG. 4. Atrophic left eye and asymmetry of skull due to bleb of the left side of head. After Bagg and Little, 1924.

FIG. 5. A litter of 8 young resulting from a mating of two *my/my* mice, showing localization of blood-filled blebs of the head region. Left and right sides of each embryo are shown. After Bagg and Little, 1924, in the *American Journal of Anatomy.*



FIGURES 1–5



FIGURES 6–9

unilateral or bilateral microtia were not uncommon. The anomalies of the limbs were very diversely comprised of syndactyly, polydactyly, hypodactyly, and severe clubbing defects, such defects being *usually unilateral*, more common on the left side than on the right, and much more frequent and *more severe in the forefeet than in the hindfeet.*

By means of extensive studies on hundreds of embryos of all stages, Bonnevie was able to trace the origin of these multiple defects to an exudation of cerebrospinal fluid beneath the skin of the neck. In normal mouse embryos of 7–8 mm. this fluid, already being formed in the myelencephalon, escapes through a transitory opening in the roof of the primitive fourth ventricle, the *foramen anterius* (fig. 1), and collects beneath the epidermis, where it is absorbed. In the abnormal Bagg-Little embryo, however, an excess quantity of cerebrospinal fluid collects in the neck region in the form of a large bleb or blister (fig. 2*a*). These primary neck blebs (*Nackenblasen*) then migrate beneath the epidermis—guided by the surface relief and conditions of tension in the embryonic skin—over the lateral portions of the head into the face (fig. 5), and over the trunk into the extremities (fig. 2*b*). Through stagnation in the concave areas, such as the orbital pits, or after arrestment at the ends of the limb buds, the increased pressure resulting from subsequent transudation of blood and lymph leads to the disruption of formative processes in their sensitive phases and hence to persisting anomalies. Wandering blebs leave scarcely any trace of their paths, these being detectable at most by a somewhat sparse growth of the hairy coat. Also, in places where gross deformities are produced through the pressure of arrested blebs, the fluid is usually wholly resorbed during the fetal period.

On the basis of Bonnevie's studies, this syndrome in the mouse was later termed "myelencephalic blebs" by Little and McPheters (1932), the recessive gene being labelled *my*. For further details and references to the extensive literature the reader is referred to summaries by Grüneberg (1943, 1947).

THE ASYMMETRIC FORM OF STATUS BONNEVIE-ULLRICH

This astonishing revelation of the formative processes responsible for multiple anomalies in Bagg-Little (*my*) mice was utilized by me in 1936 for the elucidation of very similar complexes of deformities in man. Entirely new reference points were thus established for the interpretation of a seemingly inex-

FIG. 6. Severe malformation of hand in form of symbrachydactyly, combined with unilateral Pectoralis defect. After Steche, 1905.

FIG. 7. Congenital ophthalmoplegia (combined bilateral facialis-abducens paralysis), associated with ptosis, narrowing of the palpebral fissures, and unilateral defect of the Pectoralis. After Peritz, 1912.

FIG. 8. Asymmetric form of St. B. U. in an 18 month-old boy: right-sided Facialis paresis, asymmetry of thorax, with Pectoralis defect and hypoplasia of the nipple, unilateral shortening of the arm, with brachydactyly and syndactyly of the hand, and ogive palate. After Petersen, 1939.

FIG. 9. Congenital right-sided facialis paralysis, with deformed right ear and right upper extremity. After Essen-Möller, 1928.

plicable maze of facts found in the case-history literature on congenital absence of muscles and congenital motor disturbances of the cranial nerve domain. As in all other developmental anomalies, no unitary concept of pathogenesis dared be postulated for these two groups of defects, as was evident from a purely morphological classification. However, a close relationship between certain forms of muscle defects of the trunk and congenital disturbances in the cranial nerve region could be deduced from the fact that they were not infrequently observed in combination. Furthermore, they are often accompanied by still other anomalies of a sort suggesting a common teratologic origin of the two groups of defects.

The typical *unilateral Pectoralis defects* are regularly associated with *hypoplasia or aplasia of the nipple* and a generalized atrophy of the overlying skin and its appendages (sweat glands, hair follicles). Rather frequently they are combined with more or less profound *deformities of the hand* on the same side. *Motor defects in the cranial nerve region* are likewise encountered in association with atrophy of the skin, *anomalies of the hair and sweat glands*, *ear deformities*, including microtia, and *defects of the ocular adnexa* (absence of the caruncula lacrimalis, hypoplasia of the tear glands, narrowing of the eye-slits, etc.). There are in the literature not a few cases (e.g. Gütermann, 1902; Schmidt, 1897; Spatz & Ullrich, 1931) in which the multiple defects of the head and trunk regions bear an exceptionally strong resemblance to the anomaly complexes of the *my* mouse. Especially the severe unilateral deformities of the hand (symbrachydactyly) which accompany Pectoralis defects, and the above-mentioned dysplasias of the orbital structures show an almost complete identity with the animal abnormalities clarified by Bonnevie's work (figs. 3 and 6).

With the aid of the bleb mechanism, moreover, all of the other peculiarities of the syndrome under discussion are made intelligible in a striking way. All of the developmental anomalies of the hand in their varying forms—from the "club-hand", corresponding to the embryonic hand-paddle, to the simple cutaneous forms of syndactyly—are also exhibited by *my* mice. And again, just as the *my* anomalies are more frequent and more severe in the fore-limbs, the defects of the feet in man are quite secondary to those of the hands. Nothing is known concerning unilateral Pectoralis defects in *my* mice. Since such defects in man (in contrast to the symmetric muscle aplasias) are never strictly confined to the musculature, but are usually accompanied by defects of the adjacent skin structures and sometimes even by a cleft of the underlying ribs, it has been customary to assume some arresting agent working from the outside; for example, a hammer-like pressure action of the anterior limb bud or the chin might be considered. But it seems much more reasonable to account for these developmental arrests of the Pectoralis in their many variations by the action of a cerebrospinal fluid bleb, which, in the course of its migration from the neck region into the limb bud, may come to rest in the shoulder region.

The bleb theory proves to be particularly illuminating with respect to the polymorphic nature of the anomalies found in conjunction with congenital locomotor disturbances in the cranial nerve region. Functional deficiencies in this area might be equally due to "muscle defects" or to lesions of the nerves or their motor centers (nuclear defects). The Bonnevie theory offers an explanation *par excellence* for all such possibilities of damage, inasmuch as the primary neck bleb develops over the nuclear region of the medulla oblongata and then wanders over the lateral aspects of the head into the face. Thus, there is a good explanation for unilateral facial paralysis combined with a malformed ear (fig. 9). Of great significance is the fact that in cases of "congenital nuclear damage" (Heubner, 1900) there is no primary agenesis in the strict sense. Just as in Heubner's classical demonstration, it was again apparent in a study by Spatz and Ullrich (1931) that the nuclear anlage must have been present but was destroyed at an early embryonic stage. These two important demonstrations were concerned with cases of *bilateral ophthalmoplegia* and combined *abducens-facialis paresis*. The nuclei of these two cranial nerves lie at the base of the rhomboidal sinus, at precisely the place where the primary neck blister forms, so that a pressure effect of the latter would be expected to be most strongly expressed upon these nerves.

Also explained in the finding of Schüssler and Leischner (1944) that combined VI + VII paralysis always involves a complete deficiency of the upper facial region. From the topological relations of the facialis nerve, it is apparent that mechanical pressure damage to the narrowly circumscribed region of the abducens nucleus is scarcely possible without simultaneous injury of the overlying root of the facialis. The further, infranuclear, tracts of the VI*th* and VII*th* nerves offer considerable variety in the possibilities for damage, so that isolated facialis or abducens pareses are also frequently encountered in varying forms (fig. 8).

One further important fact can be deduced independently from a survey of the published case-reports on cranial nerve defects: it is precisely the combined forms of abducens paralysis that are most commonly observed in company with the above-mentioned dysplasias of the orbital structures and also with the "typical" defects of the Pectoralis and the galaxy of associated anomalies (fig. 7). For such associations of "nuclear lesions" and peripheral developmental disturbances a most cogent explanation is provided for the first time in the theory of wandering cerebrospinal fluid blebs.

PTERYGIUM COLLI AND CONGENITAL LYMPHANGIECTATIC EDEMA

In addition to the concordance shown by the human and *my* anomalies in their final phenotypic form and in their aggregations, one can also infer from the available clinical observations a parallelism in their development extending back into fetal life. The transfer of the cerebrospinal bleb mechanism to human

beings was made particularly obvious to me in view of the fact that prior to the publication of Bonnevie's work I had called attention to the curious edematous conditions of the skin which occur as a part of the syndrome involving muscle aplasias and nuclear deficiencies. Starting from the observation of *pterygium colli* in a 6 year-old girl, I discovered from a review of the literature that the formation of such skin folds on both sides of the neck had a connection with so-called *congenital lymphangiectatic edema*, the latter being evidently a forerunner of pterygium colli. The association was described as a "typisches Kombinationsbild multipler Abartungen" (Ullrich, 1930). It included, in addition: deformities of the ears, hypoplasia of the nipples, syndactyly, and dystrophies of the nails, as well as muscle defects and motor disturbances in the cranial nerve area. Later, on extending the bleb theory to human malformations in 1936, I was able to add from the literature (e.g., Wernher, 1843) descriptions of stillborn fetuses showing massive edema of the neck region (fig. 11) of a form like that occurring in *my* mouse embryos—thus extending the similar course of phenogenesis still further backward toward its inception.

It would thus seem that the cerebrospinal bleb mechanism had been established without a gap, commencing with the time of origin of the primary neck blister. Nevertheless, I have pointed out from the beginning that such analogies based upon purely epigenetic events do not prove the presence of an identical starting mechanism. The syndrome in *my* mice has been shown to be recessively inherited; therefore, the excess oozing of cerebrospinal fluid must be conditioned by the action of the abnormal gene in homozygous state (*my/my*). Thus far no definite conclusion has been reached concerning the inheritance of the corresponding syndrome (St.B.U.) in man. Moreover, the transfer of the bleb theory to man does not, of course, demand a genetic determination of the resulting human anomalies. It is at least conceivable that purely peristatic factors might initiate the appearance of excess cerebrospinal fluid.[1]

On purely theoretical grounds, one would expect "wandering cerebrospinal fluid blebs" to produce a kaleidoscopic assortment of defects, in other words, a markedly *polyphenic* syndrome. In assigning the various clinical cases to St. B.U. it is therefore neither essential that inheritance should be demonstrated nor that an exact correspondence should be evident between the human anomalies and those shown by *my* mice. Furthermore, no single characteristic in itself can be regarded as pathognostic. Each individual patient and each anomaly-complex proposed for consideration under St.B.U. must be critically analyzed from both the clinical and phenogenetic points of view. For this purpose I regard the following criteria as significant:

[1] An observation by Liebenam (1938) on twins is of interest in this connection. In a pair of one-egg twin sisters, only one exhibited a complex consisting of unilateral absence of the Pectoralis and severe syndactyly, whereas in respect to a slight scoliosis, a slanting pelvis, and a hypoplastic high swung scapula the twins showed mirrored concordance. From this observation one can infer a strongly modifying action of intrauterine environmental factors.

1. The designation of St.B.U. should be reserved for those multiple deformities or syndromes which, in their form and distribution, are wholly explicable in terms of the bleb mechanism. Since this mechanism permits a certain freedom of expression, isolated anomalies of each type and symmetrical systemic anomalies should not be drawn into consideration here.

2. Within the general group of congenital motor defects in the cranial nerve region and congenital muscle defects it is particularly fitting to consider those involving a combination of nuclear lesions and peripheral muscle aplasias and other typical anomalies. Also, Bonnevie's theory provides the best available explanation for those cases of typical unilateral Pectoralis defects with deformities of the hand, even when unaccompanied by demonstrable anomalies in the head region.

3. A marked involvement of internal structures in any such complex of abnormalities cannot be harmonized with the bleb hypothesis except in special instances, and these must be decided with extreme caution.[2]

4. A most important diagnostic index is furnished by the occurrence of congenital edematous conditions of the neck and extremities, especially when an asymmetric distribution is evident. "Congenital lymphangiectatic edema," however, requires a careful differentiation from other edematous skin conditions of infancy.

Following my detailed formulation of its serviceability for human pathology, it was natural that Bonnevie's remarkable discovery should have been widely employed for the explanation of various syndromes of developmental anomalies. Thus many authors, with or without knowledge of my publications, have extended the circle of abnormalities to be considered under St.B.U. considerably beyond the confines which I originally proposed. Although Bonnevie's theory is especially attractive in relation to the many diverse combinations of deformities of the head and extremities, it cannot be used as a basis for unifying all of these syndromes. The criteria which I have proposed have often been disregarded in assigning individual cases and certain syndromes to St.B.U. In a recent summary paper (Ullrich, 1949) I have undertaken a critical review of this literature. The results can be summarized here only briefly, with the omission of many details.

In no case should the concept of "bleb diseases" be boundlessly extended in the manner attempted by Engel (1940). If one heeds the various criteria set forth above, it is easy to see that the bleb theory is surely misapplied in the case of Pfaundler-Hurler's disease, in Morquio's disease, in Léri's "pleonostéose familiale," in the Moon-Biedl-Bardet syndrome, and in Crouzon's form of craniofacial dysostosis and other types of oxycephaly. Apert's acrocephalosyndactyly is somewhat more pertinent since in this combination of head and limb deformities the latter strongly resemble symbrachydactyly, as observed in cases of Pectoralis defect. The "spoonhand" in Apert's syndrome would seem to be readily attribut-

[2] For example, minor developmental defects of the heart might be explained by the penetration of bleb fluid from the shoulder region into the mediastinum (Glanzmann, 1946).

able to a developmental arrest resulting from a cutaneous cerebrospinal fluid bleb. However, the decided symmetry of this condition and its constant form of expression have led me in agreement with Nachtsheim (1943) and Haase (1942) to expressly dissociate acrocephalosyndactyly from St.B.U. (Ullrich, 1943). Originally I, too, assumed a close relationship between mongoloid idiocy and the syndrome which I defined involving pterygium colli (Ullrich, 1930). Later, however, in transferring Bonnevie's findings to human anomaly-complexes, I found it necessary to revise this view (Ullrich, 1936). Mongolism, because of its generalized symmetrical character, cannot be satisfactorily explained by the bleb hypothesis.

Arthrogryposis multiplex congenita (Stern), which Heijbroek (1941) has attempted to unite with St.B.U., must be excluded as a symmetrical form of mesodermal dysplasia (Niemeyer, 1946). I am also inclined to regard as extraneous 2 cases of "cranio-carpopedal dystrophy" described by Freeman and Sheldon (1938*a*, *b*), despite the associated facial swellings, because of the symmetric nature of the defects of the extremities. Further, it is surely improper to attribute the "hereditary potato-nose" anomaly in Benjamin and Stibbe's family to the Bonnevie mechanism merely because occasional deformities of the hands appear in the family (Nieuwenhuijse, 1942).

Since pterygium colli occupies a central position in this complex of multiple anomalies and together with the antecedent congenital edema of the skin serves as a useful connecting-link between the human and animal anomalies, it is tempting to relate webbed skin formations in other parts of the body to cutaneous cerebrospinal fluid blebs. As in all other developmental defects, however, a winged-skin deformity may result from various phenogenetic causes. In particular, the unilateral or bilateral skin folds of the popliteal spaces (Kopits, 1937; Marquardt, 1938; Aberle-Horstenegg, 1938), in which there are included muscle fibers and nerve trunks, I consider to be unrelated to St.B.U. It is noteworthy that Kieser (1939) was able to demonstrate a relationship with Status dysraphicus (Bremer, 1926, 1929) in a family showing hereditary multiple skin webs, for which he proposed the more specific title, "myelo-osteo-musculo-dysplasia hereditaria." This constitutional disorder also exhibits numerous other phenotypic connections with the complex of St.B.U.: dysplasia of the nipples, funnel chest, contractures of the fingers and toes, extraocular muscle palsy, etc. Clinical differentiation of Status dysraphicus—of which the early manifestations in childhood are as yet little known—and the anomalies due to cutaneous edema can present extraordinary difficulties. However, it is my opinion that the cutaneous bleb theory is not applicable to these multiple deformities of a very different nature.

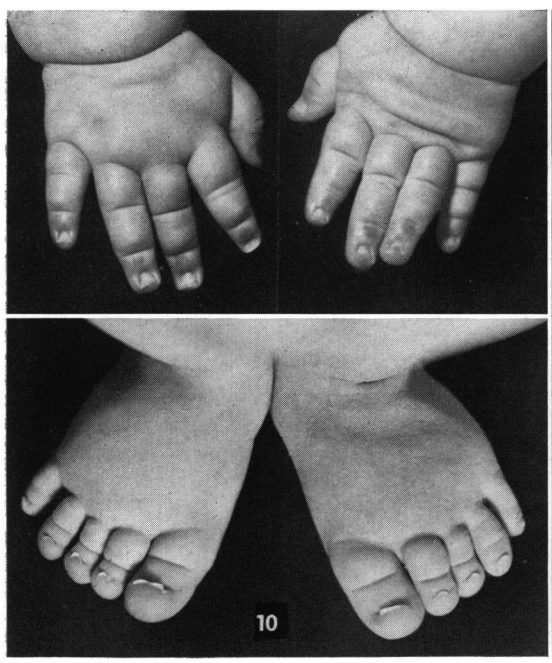
Among the congenital conditions involving fluid accumulations and stretching of the skin there are two clinical pictures which may be mentioned. They are, however, distinct from St.B.U. by virtue of an extensive involvement of the internal organs. Siegmund (1938) demonstrated in 2 sibs possessing "congenital lymphangiectatic edema" a severe deficiency of the elastic connective tissue generally. This "elastotrypsia" explained not only the looseness of the skin, but also the formation of numerous intestinal diverticula in these individuals. Under the title of "dysencephalia splanchnocystica", Gruber (1934) described a characteristic syndrome of stillborn infants in which there are hernioid changes of the brain and cyst formations of the abdominal organs, combined with anomalies of the extremities. Gruber justifiably considers the bleb hypothesis unsuited for the clarification of these complex anomalies.

THE SYMMETRIC FORM OF STATUS BONNEVIE-ULLRICH

When the developmental mechanism due to Bonnevie is not overextended in theory, but is restricted to those abnormalities which it so plausibly and simply explains, serious objections cannot be raised against its transfer to

human teratology. Nevertheless, in reviewing the pertinent literature I have reached the conclusion that a certain refinement and subdivision is necessary even within the circle of multiple anomalies which I originally regarded as relevant.

As outlined above, I originally considered congenital lymphaniectatic edema (fig. 10) as a part of the typical syndrome described in 1930, and I also regarded the medial hygromas of the neck seen in stillborn fetuses (fig. 11) as a connecting link of great importance for the extrapolation of the wandering



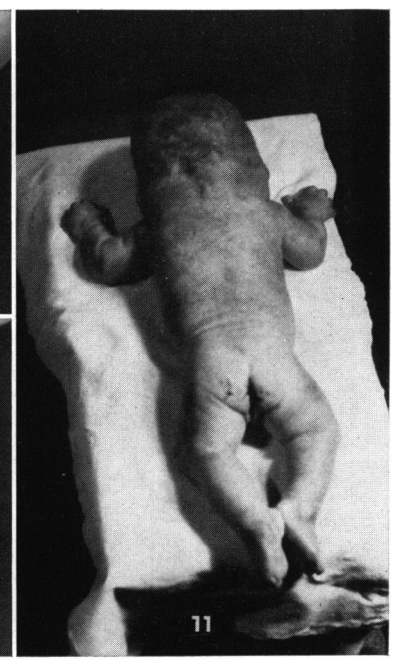


FIG. 10. "Congenital lymphangiectatic edema" of the hands and feet in a female infant, with dystrophy of all nails, especially the toe-nails. After Ullrich, 1938.

FIG. 11. Stillborn fetus with massive edema of the neck and arms. Courtesy of Prof. Rietschel, University of Würzburg Kinderklinik.

bleb mechanism to man. At that time only a few observations were available to serve as examples of the typical syndrome comprising pterygium colli. Meanwhile a large number of cases have since been described (in part as "St.B.U.") which conform without question to the syndrome which I described as a special biotype (fig. 12). The essential features of the complex were independently described above all by Turner (1938) without knowledge of my publications. On the basis of no less than 9 cases, this author characterized as a new syndrome the triad of "infantilism, congenital webbed neck, and cubitus valgus" (fig. 13). On the identity of Turner's

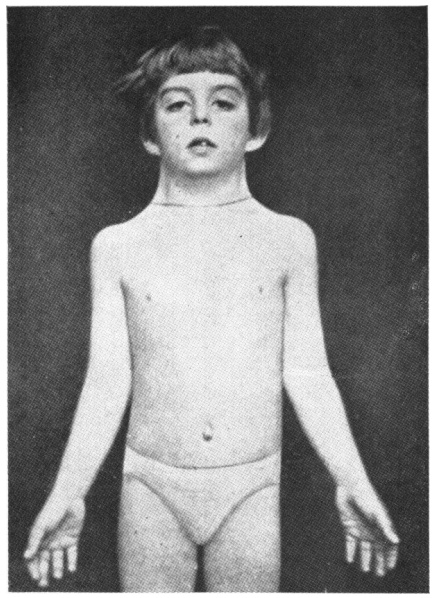


FIG. 12. "Typisches Kombinationsbild multipler Abartungen" [after Ullrich, 1930]. Symmetrical form of Status Bonnevie-Ullrich: pterygium colli, hypoplasia of nipples, deep-set ears, characteristic physiognomy, with ptosis and triangular-shaped mouth.

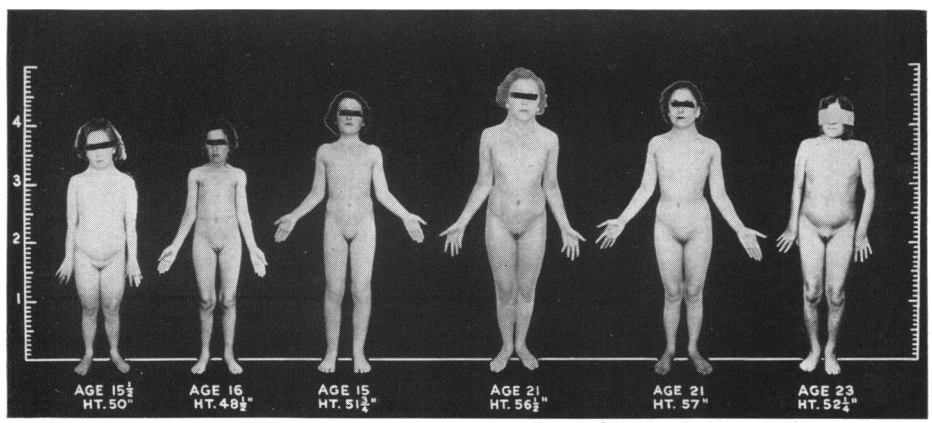


FIG. 13. Turner's syndrome: Infantilism, webbed neck, and cubitus valgus in 6 female patients. After Turner, 1938, in *Endocrinology.*

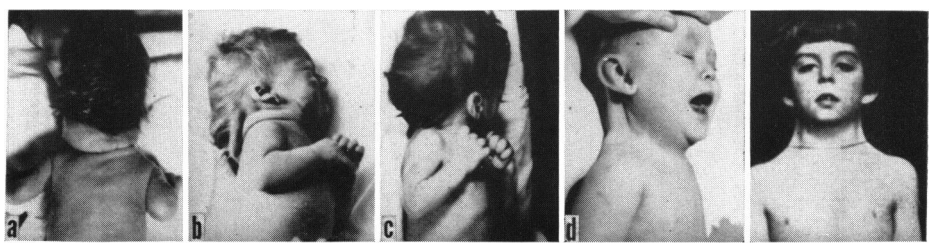


FIG. 14. Development of pterygium colli from congenital edema sac of the neck region: *a.* Female newborn with neck edema sac; *b.* Female nursling with broad loose neck folds; *c.* Female, 2 months old, with broad neck skin and diagonal folds in the region of the low-set hair line, combined with lymphangiectatic edema of the extremities and dystrophic nails; *d.* One year-old female, with broad loose neck flaps of the nape congenital lymphangiectatic edema of the hands and feet, and dystrophy of the toe-nails; *e.* (*right,* unlabeled) Eight year-old female with typical pterygium colli (original type case of "Status Bonnevie-Ullrich"). Personal observations.

syndrome and that described by myself prior to the appearance of Bonnevie's reports there can be no doubt. In the description of my original female patient with pterygium colli, mention was made of the small stature and the hypoplasia of the nipples, as well as the cubitus valgus position of the arms (fig. 12). The characteristics emphasized by Turner, on the other hand, recapitulate only some of the more conspicuous features which suffice for the recognition of the complex which I described in greater detail. Since Turner conceived the syndrome as being primarily an endocrine disorder, it is natural that less attention was accorded the less conspicuous anomalies and that the fundamental significance of the congential skin edema was not recognized.

As is so often true of newly described diseases, the further characterization of Turner's syndrome (in the American literature) and Status Bonnevie-Ullrich (in the European literature) followed somewhat different lines. Moreover, due to the limitation of scientific exchange during and since the last war, it was only very recently that the identity of the two described pictures became evident.

On the basis of this literature and further personal observations, the clinical features of this syndrome can now be summarized in the following manner:

By virtue of a relatively constant expression of its component traits, St.B.U. like other "syndromes", is distinctive among the general class of multiple anomalies. The impression created is peculiar to the syndrome alone and permits one at first glance to speak of a special "type". Foremost among the traits responsible for the singular appearance is the *pterygium colli*, the bilateral broad folds of neck skin extending from the shoulders to the mastoid processes, and the resulting illusion of a short neck. The regularly associated moderate dwarfness or *nanism*, the distinct hypoplasia of the nipples and—especially in females—the marked retardation of maturation and the *infantile characteristics* are immediately apparent. Other distinguishing features include: the looseness of the skin (*cutis laxa*), the *low hair-line* at the nape, and the *deep-set ears*; the latter usually show attached lobes and other "degenerative" characteristics, including at times an abnormal channeling of the auditory meatus. Motor defects in the cranial nerve region are hardly mentioned. In particular, there are no reports of asymmetric pareses or combined cranial nerve paralysis, such as the bilateral abducens-facialis type, which might be referred to a lesion in the nuclear area. Nevertheless, the rather languid expression of the entire face, the *sagging eyelids*, which only rarely constitutes an actual ptosis (Ullrich, 1930; With, 1935), the frequent *epicanthus*, and the deep-set corners of the mouth producing a *triangular mouth*, are very prominent. Also characteristic are the dystrophic nails which are usually found on all fingers and toes; these are markedly shortened and perpendicular, and have been described as spoon-nails or *koilonychia* (Glanzmann, 1946; Guinand-Doniol, 1947). With the ex-

ception of the pterygia of the neck, there are as a rule no other web formations, except perhaps between the fingers; numerous, though rather inconspicuous, webs of various interdigital areas have been observed only by Ostertag and Spaich (1936).

Skeletal anomalies are found principally in the head region. In addition to a constantly observed "*ogive palate*", Fanconi and Grob (1934) first drew attention to the marked development of the *impressiones digitatae* of the skull, which Rossi (1945) was able to confirm in almost all of his cases. Another almost invariable symptom in my experience is the *cubitus valgus* deportment of the arms, to which Turner drew attention. Also, a symmetric broadening of the epiphyses of the long bones ("*champignon epiphyses*") seems to be typical (Glanzmann, 1946; Morando, 1946). Unilateral skeletal defects of the lower extremities have been only occasionally encountered: Hoffmann (1937): *luxatio coxae*; Cotterman (1948) *clubfoot*; Guinand-Doniol (1947) luxatio coxae and clubfoot.

Involvement of the internal organs, apart from the gonads (see below), appears to be entirely in the background in the syndrome which constitutes the symmetrical form of St.B.U. Hofmann (1925) assumed the presence of a septal defect in a patient having a systolic murmur; pathologic cardiac findings were also mentioned by Hamne (1948) and Nageotte-Wilbouchewitch (1934). The kidney anomaly in Dreyfus' (1936) case, in which there was assumed to be congenital lues and rachitis (renal form?), need not be related to the syndrome.[3] In contradiction to Rossi and Guinand-Doniol, a review of the entire literature reveals that there is no marked psychic underdevelopment as a rule. The intelligence can indeed be above average in some cases (Turner, personal observations).

At birth, many cases show edematous swellings of the neck and extremities, which gradually subside in the course of the first few months or years. At this early stage, the superfluous skin of the neck region has not yet assumed its final characteristic form. Loose, flabby folds or sacs of skin occur over the nape and throat, and the gradual transformation of these into a typical bilateral pterygium (fig. 14) has been observed in one and the same patient in several instances (Rossi, personal observation). Similarly, there is often a marked edema of the hands and feet or both (fig. 10), which, after its regression, leaves the skin of the fingers and hands (toes and feet) "too loose". Thus, cases described in the literature as "congenital lymphangiectatic edema" can be assigned to the syndrome after careful differential diagnosis with respect to other edematous skin conditions of the newborn.

In a summary paper now in press (Ullrich, 1949), I have assembled from the

[3] It is noteworthy that kidney anomalies occurred in combination with the typical superficial anomalies in several stocks derived from Bagg and Little's mouse strain. Whether these urogenital defects were actually due to the *my* gene was never conclusively determined (Grüneberg, 1947).

German-language literature (including a portion of the observations on "Turner's syndrome") more than 50 cases of St.B.U. This permitted me to strengthen a conclusion already hinted in an earlier paper (Ullrich, 1943), namely, that the syndrome which had at first seemed to me so convincing could no longer be reconciled with an unqualified theory of wandering cerebrospinal fluid blebs. Making use of the criteria listed above, it will be seen that there are unmistakable contradictions from several points of view.

Although the centrally-produced motor defects of the cranial nerve region combined with asymmetric muscle defects and other malformations can be effortlessly aligned with "typical St.B.U.",[4] the constitutional complex corresponding to Turner's syndrome cannot be satisfactorily explained by the wandering bleb mechanism. Thus, the dwarfness, which in older patients is accompanied not only by hypoplasia of the nipples but also by generalized infantilism, cannot be explained without postulating certain ancillary hypotheses which are not at present justified. But above all, the decided symmetrical character of the syndrome comprising pterygium colli stands in clear contradiction to the theory. In fact, it is scarcely conceivable that more or less accidental wandering of cerebrospinal blebs could lead to a symmetrical dystrophy of all fingernails and toenails, as is not uncommonly observed. These facts are not depreciated by the occasional finding of unilateral anomalies, such as foot deformities and dislocation of the hip. Furthermore, the clinical findings in the symmetric form of St.B.U. deviate from the conditions found in *my* mice in that the edema in the former is not dissipated until the first few months or years of life, whereas the cutaneous blebs of *my* mouse embryos are fully resorbed *in utero*. Conversely, in the typical or asymmetric form of St.B.U., there are no cases known to me of edematous skin conditions of the newborn.

These considerations point to certain discrepancies between the asymmetric form of St.B.U. and the symmetric form which is characterized by pterygium colli. Even though such differences might not seem very deep-seated and perhaps even reconcilable, there is one further striking fact which points to a difference in the genetic basis and embryological mechanism: the syndrome including pterygium colli shows a strong predilection for the female, whereas no equally strong bias is evident in the asymmetric syndrome. Among 60 definite cases of pterygium colli and congenital lymphangiectatic edema, I find the sex ratio to be 48 ♀ : 12 ♂. One must consider the possibility that this preponderance of females may result from a preferential recording of female cases due to the more pronounced character of the syndrome in this sex, especially in older patients where there is an evident mammary hypoplasia and sexual underdevelopment. However, this seems to be excluded, since even in

[4] This group has been augmented by important recent observations by Petersen (1939), Schüssler and Leischner (1944), Liebenam (1938), and others.

early childhood females outnumber male cases in the ratio 9:1, and among 13 cases of "congenital lymphangiectatic edema" summarized by Volz (1938), only 3 cases are male, 2 cases being of unspecified sex (table I).

A similar gynectropy, which certainly cannot be ascribed to chance, holds for the cases described under the title of "Turner's syndrome." After writing my more extensive review (Ullrich, 1949), I was enabled through the kind assistance of Dr. C. W. Cotterman to make a survey of the literature from America and other lands:

Martin (1947) gives the sex ratio for Turner's syndrome as 9 ♀: 1 ♂, and Greenblatt and Nieburgs (1948) report their male patient as being the only exception known to them of the rule that the disease is confined to females, excepting one earlier report by Flavell (1943). However, in the same year Dorff *et al.* (1948) and Foucar (1948) reported two additional male cases, and Foucar cites male patients reported by Sylvest (1940) and Bizzarro (1938). However, the great majority of the described cases are female (Schneider & McCullagh, 6 cases; Turner, 9 cases; Allesandri *et al.;* Greenblatt & Nieburgs' case #1; With; Sharpey-Schafer; Morando; Capurro; Hamne; Shreshevski, 5 cases; Slonimski). It is also noteworthy

TABLE 1. THE SEX DISTRIBUTION IN STATUS BONNEVIE-ULLRICH

REPORTED CASES	FEMALES	MALES
Symmetrical form of Status Bonnevie-Ullrich		
Adults and older children	31	8
Infants and young children	9	1
	40	9
Congenital lymphangiectatic edema (cases of Volz)	8	3
Total	48	12

that the male cases recently added to the literature seem to show a somewhat milder expression of the syndrome (Foucar, Martin, Bizzarro; Martin's own case, however, must be excluded as a case of Klippel-Feil syndrome).

In view of these considerations the question arises as to whether the syndrome comprising pterygium colli, which includes Turner's syndrome, should in any event be classified with St.B.U. In my opinion this may be answered in the affirmative, since the developmental origin of the majority of the anomalies must be referred to fetal edematous conditions of the skin. The question remains, however, whether we are dealing here with "cerebrospinal fluid blebs". To be sure, it is tempting to attribute the massive collection of fluid which gives rise to the pterygium colli to an escape of fluid from the foramen anterius, inasmuch as the latter structure has been demonstrated in the human embryo (Bonnevie, 1934). On the other hand, experimental embryological studies in animals have shown that the formation of unusual skin blisters, which seem to play a role in the etiology of many kinds of anomalies, are not exclusively derived from expressed cerebrospinal fluid.

I shall refer here only to the very careful studies of Sturkie (1941), who was able to trace the origin of naked areas on the head of the domestic fowl to epidermal blisters in the chick embryo, and to the remarkable "blood blisters" of the tips of the tails which Kaven (1943) demonstrated in fetuses of a strain of mice having kinky tails with wedge-shaped vertebrae. Also in Dunn's *st* mutation (1934), a simple recessive form of brachyury combined with locomotor disturbances and deafness, the newborn mice show peculiar blood-filled blisters over the crown of the head and in the neck region. These were subsequently shown by Bonnevie (1940) to arise in a manner entirely different from that of the cerebrospinal blebs of *my* mice.

The developmental physiological theory of Blechschmidt (1947, 1948) also seems worthy of mention in this connection. This anatomist regards conditions of tension in the epidermis, resulting from fluid accumulations within the embryo, to be a fundamental determinant of the general body form. He presumes that the amnionic fluid derives from the embryo by a process of active epithelial transudation, in which the ends of the extremities and the axillae are differentiated as areas of especially active transfer. In personal communication with Prof. Blechschmidt I am told that severe edematous conditions of the neck are "not infrequently" seen in human embryos. The confirmation and further elaboration of Blechschmidt's theory remains for the future.

In any case, it is clear that events other than an oozing of cerebrospinal fluid may lead during embryogenesis to the formation of circumscribed areas of cutaneous edema. In the present stage of the study, I am inclined to regard an autochthonous formation of the skin swellings as a much more probable mechanism for the phenogenesis of pterygium colli than that of wandering "myelencephalic blebs". Since such a mechanism would be not entirely divorced from that of Bonnevie, I do not regard a change in the nomenclature as necessary. Even in the "asymmetric form of St.B.U." it is possible as previously discussed that the phenogenesis is not wholly concordant with that of *my* mice back to the stage of exudation of fluid through the foramen anterius. An autochthonous origin of subcutaneous fluid in symmetrical St.B.U. or Turner's syndrome would imply only that the parallel course of development takes its start at a somewhat later point in prenatal life. Serving to suggest a later teratogenetic determination point, indeed, is the fact that the edematous swellings tend to remain even after birth in the case of the symmetric syndrome, and also the fact that the anomalies produced in the latter tend to be somewhat less severe than those which characterize the asymmetric form of St.B.U.

More important than the problem of nomenclature is the certain conclusion that the establishment of two different phenogenetic mechanisms requires that the two clinical pictures be kept separate for the purpose of further genetic and embryological studies. For such studies a genetically uniform substrate is, of course, an unconditional prerequisite. In contrast to the extremely polymorphic nature of the asymmetric form of St.B.U., the syndrome involving pterygium colli is so relatively uniform and characteristic that the diagnosis can ordinarily be accurately made on first examination. Essentially only three

other anomaly-complexes come into consideration in the clinical differential diagnosis, viz., mongolism, Klippel-Feil syndrome, and Status dysraphicus.

Transitional cases of *mongolism* may arise from the fact that in this disease there is usually a cutis laxa and a loose nape skin which occasionally even takes the form of a typical pterygium colli (Ullrich, 1930). Nevertheless, mongoloid idiocy is not only distinguished by a marked involvement of the internal organs but is also distinct in showing no sex preference. Clinically the differentiation will usually be possible from the fact that mongolism shows a highly characteristic behavior pattern with feeblemindedness, which is at least not obligatory in St.B.U.

Klippel-Feil syndrome presents a less clear basis for separation from both the phenogenetic and the clinical point of view. The distinction would, of course, be superfluous if a subcutaneous edema mechanism should prove responsible for this condition as well. On purely mechanical grounds one can well imagine a fusion of the cervical vertebral bodies in consequence of the pressure of a primary neck bleb. I regard this possibility, however, as unjustified. It is true that Klippel-Feil syndrome is not uncommonly accompanied by other anomalies similar to those found in St.B.U. (Rinvik, 1944). However, the central feature of Klippel-Feil syndrome is a localized developmental failure of the vertebrae, and this may occur in other cases in sections of the vertebral column other than the cervical region, in such a way that cerebrospinal blebs could not plausibly explain the state of affairs. Also, it must be noted that here again, as in mongolism, there is, to my knowledge, no marked predilection for the female sex.

It should be mentioned that Gilmour (1941) found *iniencephaly* more common in females than in males. This severe defect of the occipital region, which is incompatible with life, no doubt stands in close morphologic relationship with Klippel-Feil syndrome (Drachter, 1923). This is not to say, however, that it represents a specially severe manifestation of the same phenogenetic disturbance. Kaven (1943) also mentions that the female seems to be more severely affected in the case of the short-tailed anomaly of the house mouse, which is accompanied by blood blisters and vertebral deformities very similar to those in Klippel-Feil syndrome. All of these developmental anomalies of the axial skeleton are nevertheless far removed from the anomaly complex of *my* mice, and are presumably brought about through entirely different pathogenetic events. Finally, it may be mentioned that von Pfaundler's (1939) extensive studies on "Frühtod, Geschlechtsverhältnisse und Selektion" showed that developmental anomalies in general constitute almost the sole cause of intrauterine death for which there is a marked excess of female cases.

For genetic purposes, at any rate, it is advisable at present to separate Klippel-Feil syndrome from St.B.U. In general these two conditions are not difficult to distinguish clinically. Even without roentgenograms a synostosis of the vertebrae is usually apparent in these "hommes sans cou" by virtue of the reduced mobility of the neck, whereas in St.B.U. the head is freely mobile and the shortness of the neck is only an illusion due to the broad skin flaps. The broad neck in Klippel-Feil syndrome is admittedly not always due to lateral muscle-wings; there are sometimes "pure skin" folds of the sort seen in Turner's syndrome (Frawley, 1925; Martin, 1947). Although the low hair-line of the neck and the abnormal ears also agree with the features of St.B.U., cases with demonstrated vertebral changes should be separated from Turner's syndrome, rather than to designate such as combinations (Martin).

The greatest difficulties can arise in the clinical differentiation of St.B.U. and *Status dysraphicus*. Since the basis for the latter condition lies in a malformed defective closure of

the medulla which affects principally the dorsal marginal portions of the central canal throughout its length, there is no phenogenetic resemblance to St.B.U. Also, it is not possible to unify the two on the assumption that, in accordance with Bonnevie's view, cerebrospinal fluid may also escape from places other than the foramen anterius. All in all, the phenomenology of Status dysraphicus is not explicable on a subcutaneous edema mechanism. We are therefore faced only with a phenotypical overlapping of two syndromes, which, however, may be at times very extensive (Bremer, 1926; Passow, 1933). In individual cases a differential diagnosis may have to be based upon family studies. For example, I consider one of the families reported by Rossi and Howald (1947) in their paper on the genetics of St.B.U. to be an example of Status dysraphicus. The 18 year-old proposita with funnel chest shows a typical pterygium colli, but lacks infantile features, and the 2 brothers who show milder defects (funnel chest, clinodactyly) correspond much more closely with Status dysraphicus.

INHERITANCE

Up to the present time the available publications on the inheritance of St.B.U. have not taken account of the division which has now become apparent between the two phenogenetically distinct forms, nor have other confusing syndromes always been carefully excluded. For this reason the conclusion of Rossi and Howald (1947) that we are dealing with a facultative dominant gene cannot be definitely accepted. The first kindred adduced by these authors in evidence of the genetic pattern is, in all probability, an example of Status dysraphicus, as remarked above. In a second family, the proposita shows the typical symmetric syndrome with pterygium colli, while a paternal female half-cousin was said to show distinct signs of St.B.U. (lateral neck folds). Another pedigree previously reported by Rossi (1945) is concerned with a child with right-sided Pectoralis defect and "dorsal pads of the hands"; in the father polydactyly was present, and among the maternal relatives hypertelorism was found in several members belonging to three generations. The pedigree also shows a diabetic diathesis. This very cursory report may be retained for the genetic analysis of the asymmetric form of St.B.U., but the data should be restricted to the immediate sibship of the proposita.

Teveli (1930) recorded webbing of the third and fourth toes in the father of his patient. Ostertag and Spaich's report (1936) concerns a discordant pair of monozygotic twin brothers, one of whom showed the typical syndrome with pterygium colli and the other only *impressiones digitatae* and webbing of the second and third toes. Whether these minor anomalies, which are so frequent in the general population, can be regarded as "microforms" of the syndrome cannot be decided at present. In a brief discussion note, Baumann (1945) mentions three sibs who showed congenital lymphangiectatic edema, apparently without other anomalies. In a typical female case of pterygium colli, Cotterman (1948) found strabismus and epicanthus occurring as isolated anomalies in a brother, the mother, and a maternal cousin. Foucar (1948) cites the occurrence

of pterygium colli in two sisters described by Frawley (1925); these cases, however, are more probably Klippel-Feil syndrome.

This is all that is now available in the way of family reports. Obviously no clear evidence of inheritance can yet be claimed. Additional more extensive family studies are urgently needed, and these should not be difficult to obtain for the typical symmetric syndrome which includes pterygium colli. This easily recognized, and not exceptionally rare, complex is sufficiently homogeneous to serve well for such studies. For the typical or asymmetric form of St.B.U. the selection of propositi presents difficulties of a serious nature. However, since the purely *epigenetic process* of excessive exudation of cerebrospinal fluid is apparently responsible for these anomalies, the question of the mode of inheritance need not be posed in an overall sense.

For the symmetric form of St.B.U. or Turner's syndrome, a further investigation of the phenogenetic mechanism is also needed. We do not yet know in what way the symmetric accumulations of fluid arise in the integument. Also, the cause of the infantile dwarfness is not yet certain. An isolated impairment of the hypophysis through the pressure effect of a bleb derived from the neck region (Engel, 1940) seems highly improbable. As several authors have pointed out, the dwarfness of Turner's syndrome shows some distinct clinical differences from that of pituitary dwarfness (Schneider & McCullagh, Sharpey-Shafer, Greenblatt & Nieburgs, Flavell). Holmer (1948), as well as Schneider and McCullagh, assumes a primary disturbance of the gonads. In agreement with the increased urinary excretion of gonadotropic substances, a better therapeutic effect has been obtained with estrogenic hormones than with pure pituitary preparations. In histological studies of their patients, Atria and Donoso (1946) and Moss and Menk (1949) found the hypophyses essentially normal, whereas the ovaries showed regressive changes. Greenblatt and Nieburgs' male patient had a large penis and small testes, showing histologically a tubular hypoplasia with seemingly increased numbers of interstitial cells.

Neither a disturbance of the hypophysis or of the gonads, however, can serve as an adequate explanation of the syndrome in its entirety. The intimate interrelationships of these endocrine glands makes difficult an analysis of the exact nature of the endocrine disturbance, which must certainly play a part in this syndrome. However, endocrine disorders must, in any case, be of secondary significance in the phenogenesis of the syndrome as a whole. The beginning of the teratologic determination period must be placed at an early embryonic period; as yet there is no clear proof that ontogenetic events at this time may depend upon the endocrine system as in extrauterine life. It would not be contrary to this view, however, to suppose that some disturbance in the important organizer field of the mid-brain area might be responsible for the syndrome. It is very likely that other combinations of head and extremity anom-

alies—the so-called dyscranio-dysphalangias—may also be centrally controlled through disturbances in this region.

SUMMARY

The mechanism of wandering cerebrospinal fluid blebs discovered by Bonnevie in embryos of the Bagg-Little mouse mutant *my* ("myelencephalic blebs") may with full justification be applied to corresponding complexes of multiple anomalies in man.

By means of this theory a fully satisfactory explanation is afforded for the first time for nuclear lesions in the medullary portion of the brain-stem (nuclear aplasia) combined with (unilateral) Pectoralis defects and numerous associated deformities.

Since motor disturbances in the cranial nerve region and peripheral muscle defects are also observed in combination with lateral skin folds of the neck (pterygium colli) arising from congenital skin swellings (lymphangiectatic edema), it is natural to regard the various multiple anomalies accompanying pterygium colli as the equivalents of those present in *my* mice.

This complex of abnormalities described by me in 1930 has received increasing attention in the German-language literature under the designation of Status Bonnevie-Ullrich (St.B.U.). It is identical with a typical syndrome defined by Turner (1938).

From an analysis of all described cases it is evident that pterygium colli and its numerous allied anomalies is almost invariably associated with dwarfness and conspicuous infantilism in older female patients. The complex is strongly preferential for the female (4 ♀ : 1 ♂). This, plus the fact that there is a rather consistent symmetrical distribution of all of the defects, makes the syndrome incompatible with the wandering bleb mechanism. The latter leads one to anticipate a very polyphenic syndrome, with an asymmetric distribution of peripheral defects, like those found in typical (unilateral) St.B.U., as well as in the anomaly-complex of *my* mice.

In the symmetric form of St.B.U. one must think of an autochthonous origin of subcutaneous fluid accumulations which must account for the greater part of the abnormalities, just as in the typical or asymmetric conditions. The infantile dwarfness and the predilection for the female sex cannot be adequately explained at present.[5] The early teratogenetic time of determination, however, allows one to attribute at most a secondary significance to organ-controlled endocrine disturbances.

[5] Important in this regard is the demonstration of trophic pathways between the diencephalic sexual center and the sacral and lumbar centers. This nervous pathway, consisting of many neurones, apparently becomes united via the bundle of Schütz at the base of the rhomboidal sinus to the fasciculus parependymalis, which courses as a longitudinal tract through the substantia gelatinosa of the spinal cord (Krücke, 1949).

Since it appears necessary to modify the myelencephalic bleb theory for the symmetric form of St.B.U., which includes Turner's syndrome, and to postulate here a somewhat different edema mechanism, the two clinical pictures should be kept apart for purposes of genetic study. In this connection it is also necessary to differentiate the symmetric form from other syndromes having manifestations which sometimes overlap those of St.B.U. Difficulties in the differential diagnosis are especially furnished by some cases of Klippel-Feil syndrome and Bremer's Status dysraphicus.

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