Phenocopies

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Phenocopies by Heat Treatment

Goldschmidt (1935) proposed the concept of phenocopy for what he thought to be 21 different types of abnormal wings and 10 different types of abnormalities of bristles, eyes, and other organs produced by heat treatment of Drosophila larvae. He expressly stated: 'The enumeration shows already that the phenotypes of the great majority of mutants known in Drosophila can be produced in these experiments as non-genetic modifications. I do not doubt that in fact any phenotype of any mutant may be copied in this way if we succeed in creating still more possibilities of influence by further modifications of experimental conditions.'

Even earlier, Zeleny (1923), having demonstrated the effects of temperature differences on the phenotype of the bar eye mutants of Drosophila clearly stated 'The gene ultrabar has the same type of reaction as a temperature difference'. In F. Fischer's earlier experiments (1895) on butterflies, heat produced wing patterns identical to that of a known geographic variety. Fischer referred to this effect as 'transmutation'. One reason why similar results have not been attained in mammals is probably the smaller range of temperatures compatible with survival in warm-blooded animals than in insects.

The similarity between genetic phenotypes in Drosophila and their heat-induced phenocopies may in part be explained by heat inactivation of enzymes.

Heat inactivation of genetic enzyme variants at temperatures compatible with survival is well-known from many microorganisms, particularly from E. coli, but also from Neurospora, Primula sinensis, rabbits, and Siamese cats. In E. coli there are also temperature sensitive mutants of the lac-operon regulator gene and of a gene controlling initiation of chromosomal replication (for references see Bresch and Hausmann, 1970).

Heat instability is also a feature of several genetic haemoglobin variants in man (Genova, Turin, Bibba, Hammersmith, Sydney) usually associated with inclusion body anaemia. The heat effect in these cases, however, is important for diagnosis in vitro rather than for clinical manifestations. Furthermore, heat sensitivity is found in several variants of glucose-6-phosphate dehydrogenase (Chicago, Ohio, Oklahoma, Duarte, Albuquerque, Eyssen), associated with spontaneous haemolytic anaemia.

High temperature does not appear to induce clearcut phenocopies in mammals. No association between fever during the first trimester and malformation of the infant has been found. Virus infections with a rise in temperature to at least 38°C have been found in 2.7% of 342 pregnancies resulting in malformed children and in 2.5% of 8533 pregnancies resulting in non-malformed children (Villumsen, 1970). The incidence of bacterial infections in the first trimester in the same material was 1.8% for malformed children and 2.9% for non-malformed children.

Hypoxia and Abnormal Implantation

Büchner (1958), produced a variety of malformations in various amphibian and avian species by hypoxia. Similar to Goldschmidt's assumption (1935) for Drosophila he felt that in man 'each genetic malformation can be copied by one caused exogenously'; thus, Büchner continues, 'exogenous malformations are in principle phenocopies of malformations which may also be genetic'. This idea has not received any firm support from observations in man. Various attempts to link poor implantation, bleeding, or general anaesthesia in early pregnancy with hypoxia and consecutive malformations have been unsuccessful (see Villumsen, 1970).
Phenocopies

There is no statistical evidence nor any evidence in selected cases that hypoxia induces the same types of malformations in human embryos which, as a rule, have a genetic basis. Grebe (1954) in a review on 'Genes and phenocopies in the aetiology of human malformations', has discussed phenocopy in relation to mongolism, anencephaly, cleft lip and palate, and limb malformations. None of these examples of presumed phenocopies is convincing.

Abnormal implantation has been thought to be a cause of hypoxia and malformations. The evidence is, at best, indirect. The most clearcut type of abnormal implantation, i.e., extra-uterine pregnancy, is commonly associated with gross deformities of clearly exogenous mechanical origin quite different from any genetic syndrome or from true developmental malformations (von Winckel, 1902; Lelling, 1938). There is no evidence that extra-uterine pregnancy might produce phenocopies, and the same is probably true for other types of abnormal implantation.

Induction of Phenocopies by Chemicals

Rapoport (1939) has produced morphological abnormalities in Drosophila similar to mutant phenotypes by adding various chemicals, especially salts of metals, some of them known to be enzyme inhibitors, to the food. He tested only one stock of Drosophila and found specific effects associated with specific chemicals. More detailed studies comparing chemical phenocopies in Drosophila with known mutants have been published by Gloor (1947), Bodenstein and Abdel-Malek (1949), Sang and McDonald (1954), and Goldschmidt and Piter-nick (1957). When Goldschmidt and Piternick (1957) studied the genetic background of borate-induced phenocopies in Drosophila they were inclined to attribute the conspicuous genetic differences observed between stocks to common subthreshold mutants brought out by borate. A similar argument may be applied to heat-induced phenocopies which also vary with the genotype of the experimental animals. Heat sensitive enzyme variants may be conceived as products of genes which are subthreshold under ordinary conditions.

Landauer (1957 and 1958) has been able to produce the rumpless phenotype in chickens by insulin, boric acid, or pilocarpin. The results varied with the genotype. Landauer thinks the term phenocopy is inappropriate for cases in which the recessive gene for rumplessness becomes apparent through chemical teratogens. He prefers to reserve the term 'phenocopy' for experimentally produced conditions identical in phenotype and, at least in part, in developmental pathway to a genetic condition. Rubella embryopathy, according to Landauer (1959), should not be called a phenocopy. In Ancel’s monograph (1950) on chemical induction of malformations in vertebrates the word phenocopy appears neither on the five contents pages, nor on the four pages of the index. Thus confusion is avoided.

Defects of the caudal spine similar to rumplessness in chickens are known also in man. The more extensive defects which include not only the sacrum but several lumbar and sometimes even thoracic vertebrae are sometimes associated with maternal diabetes (Ghiai, 1972; see Figs. 1, 2a, and 2b).

Fig. 1. Agenesis of sacrum in the child of a diabetic mother. (By courtesy of Professor von Harnack, Universitäts-Kinderklinik, Düsseldorf.)
Between 1935 and 1957 Goldschmidt's use of the term phenocopy underwent considerable change, which has not been generally realized, for he often failed to clarify to what he was referring. He applied the term phenocopy rather indiscriminately to: (1) phenotypes produced by environmental factors in a genotype otherwise not associated with the same phenotype, if the same phenotype also occurs on a genetic basis without the environmental factor; (2) phenotypes produced by environmental factors, but so far unknown in other genotypes; (3) phenotypical effects of specific genes, when these are only apparent under certain environmental conditions and identical with the usual phenotypical effects of other possibly isoallelic genes.

Many medical authors have followed this vague and conflicting nomenclature (eg, Büchner, 1958; Degenhardt, 1958).

Henke, von Finck, and Ma (1941), studying heat modifications in Drosophila made a distinction between true phenocopies, in which the environmental agent affects the same developmental phase as the gene (the effect of which is copied) and false phenocopies, in which only the end result is identical.

A similar point of view is expressed by Hadorn (1955), who defined phenocopy on the basis of two strict criteria: (1) identity in all details of the pattern of phenotypical manifestation with a locus specific genetic pattern; (2) identity of the developmental path leading to the trait.

Nachtsheim (1957 and 1961) defended the rather vague application of the concept of phenocopy. His main argument was that it is not usually possible to trace the origin of a genetic trait in man, so the question whether a phenocopy is a true or a false one has to be left open.

With increasing precision in description and diagnosis of genetic entities, a wider use of the term phenocopy in man has become dubious, if not obsolete. Nachtsheim (1961) discussed epilepsy, haemophilia A and B, afibrinogenaemia, and deficiencies of clotting factors V, VII, and X as genetic conditions which may also be phenocopied. Obviously, supposed phenocopies of these conditions are identified by single symptoms rather than by the total pattern of the disease. Many more symptoms have either a genetic or an environmental cause or combined causes; to use the term 'phenocopy' to refer to this well-known medical fact no longer serves any useful purpose.

In the third edition of his catalogues of Mendelian inheritance in man, McKusick (1971) lists 943 autosomal dominant, 783 autosomal recessive, and
150 X-linked phenotypes. It is quite obvious to anyone acquainted with any of the fields of medical genetics that, at best, true phenocopies are established in an almost negligibly small minority of these conditions, and that there are no specific reasons to suspect phenocopies for almost every well-defined monogenic entity. This is not unexpected for monogenic phenotypes are basically molecular diseases or polymorphic variants. Environmental influences rarely affect only one gene product and even when they do, there is still the difference between the permanent genetic block and the temporary and variable block brought about by inhibitor substances or heat inactivation.

At first glance, vitamin deficiencies would appear to be good candidates for phenocopies. One might expect that environmental lack of a vitamin would produce the same effect as a genetic block of its resorption, metabolism, or attachment to the protein apoenzyme. The similarity between vitamin D deficiency rickets and pseudo-vitamin D deficiency rickets is striking. However, this is a rather special case; deficiency of one vitamin does not usually occur without deficiencies of other vitamins or other dietary constituents and is not usually permanent, as is the genetic block.

Phenocopies may also be expected to occur in endocrinological disorders. Most endocrine functions are limited to one or a few glands which, with the exception of the gonads, have no known function other than that of producing hormones. Hormone production may be defective either because one of the genetic biochemical links is missing, or because some external agent may have damaged a particular gland. Two examples are listed in Table I.

**Table I**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Genetic Prototype</th>
<th>Phenocopy</th>
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<tbody>
<tr>
<td>Panpituitary dwarfism</td>
<td>Autosomal recessive (Rimoin et al., 1968)</td>
<td>Birth trauma</td>
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<td></td>
<td>X-linked recessive (Rimoin and Schimke, 1971)</td>
<td>Bierich (1965)</td>
</tr>
<tr>
<td>Pendred’s syndrome</td>
<td>Autosomal recessive-defective organification of iodide with deafness (Harnack et al., 1961)</td>
<td>Endemic cretinism due to environmental iodine deficiency (Konig, 1968)</td>
</tr>
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</table>

The similarity between the two genetic types of panpituitary dwarfism and that caused by birth trauma to the pituitary body (Bierich, 1965) is striking. A somewhat similar phenotype may also be the consequence of emotional and nutritional deprivation (Silver and Finkelstein, 1967). As in genetic and traumatic pituitary dwarfism these cases show retardation of growth in height, bone age, and sexual maturation. There may be some metabolic features indicative of pituitary failure, but there are distinctive marks of deprivation dwarfism such as voracious appetite and an increase in weight and height, shortly after the psychological situation has been improved.

Pendred’s syndrome and endemic cretinism share two main symptoms—deafness and goitre. Mental deficiency and low stature, prominent in endemic cretinism, are absent or rare in Pendred’s syndrome. Still, it is tempting to speculate that the association of deafness and goitre in both diseases is due to a similar mechanism, i.e., the lack of iodine in the inner ear and in the thyroid.

In their comprehensive book, ‘Genetic disorders of the endocrine glands’, Rimoin and Schimke (1971) are very open-minded towards the possibilities of phenocopies. Table II cites some examples from their article.

**Table II**

<table>
<thead>
<tr>
<th>Genetic Condition</th>
<th>‘Phenocopy’</th>
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<tbody>
<tr>
<td>Autosomal recessive: Schmidt’s syndrome (polyendocrine deficiency syndrome)</td>
<td>Virus infection? autoantibody formation?</td>
</tr>
<tr>
<td>X-linked dominant, autosomal dominant: decrease of thyroxine-binding globulin</td>
<td>Cirrhosis, nephrotic syndrome, malabsorption states</td>
</tr>
<tr>
<td>Autosomal recessive or X-linked recessive: 18-dehydrogenase deficiency (hyperaldosteronism)</td>
<td>Drug induced (heparin)</td>
</tr>
<tr>
<td>Autosomal recessive: Bartter syndrome</td>
<td>Sodium depletion by chronic laxative abuse</td>
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</tbody>
</table>

The external causes of the polyendocrine deficiency syndrome are not well established. The other examples are obviously copies of single signs rather than of disease patterns. Generally, phenocopies are rare, and play a minor role in practical medicine and genetic counselling. They are, however, most important as models which might help to elucidate the pathways of gene action.

**Genetic Limb Malformations and Thalidomide Phenocopies**

No phenocopies are known for most types of monogenic limb malformations found in man, such as split hand and split foot; the various types of brachydactyly, polydactyly, and syndactyly; the
genetic types of peripheral defects, and many other complex syndromes. There are, however, several specific genetic types of bone defects and of triphalangy of the thumb which are sufficiently similar to some thalidomide cases to make a discussion of the phenocopy concept meaningful. The following seven types will be selected for discussion.

1. Autosomal dominant aplasia of the radius (Holt-Oram syndrome).
2. Radius aplasia—thrombocytopenia syndrome.
3. Fanconi’s pannymelopathy.
4. Roberts’ syndrome (tetraphocomelia with cleft lip and palate).
5. Pseudothalidomide syndrome.
6. Tibia aplasia with triphalangy of the thumb.
7. Triphalangy of the thumb.

Types 1, 6, and 7 are autosomal dominant, the other types are autosomal recessive. The morphology of the individual bone defects as well as of their associations in types 1, 3, 6, and 7 is very much the same as in many thalidomide cases. Not all thalidomide cases, however, are phenocopies. Complete absence of the arms, some forms of bony syndactyly of the fingers, proximal femoral defects, total or subtotal defects of all of the long bones of the legs, aplasia of the first toes, etc. do occur in some thalidomide cases, though not in any of the seven types listed above nor in any other monogenic phenotypes in man. Cardiac malformations may be associated with types 1, 2, and 3 and renal malformations with type 3. However, some more severe cardiac defects and other internal malformations—comprising duodenal stenosis, aplasia of the gallbladder, aplasia of the appendix, uterus bicornis, etc.—do occur in many severe thalidomide cases, but not in most of the seven genetic prototypes. The association of thalidomide limb deformities with anotia, abducens and facial paralysis, microphthalmos and coloboma has no counterpart in any known genetic syndrome. The midfacial haemangiomia, on the other hand, may be seen in types 1, 2, and 4.

The spectrum of each of the seven genetic prototypes is much more restricted than that of thalidomide embryopathy. Thalidomide embryopathy is not a single syndrome, definable on the basis of its component symptoms, but a teratogenic series of interconnected syndromes. Cases of thalidomide embryopathy with exactly the same time of intake constitute well-defined syndromes: such as a syndrome of anotia, facial and abducens paralysis, dysplasia of the sacrum, and ectopic kidney following thalidomide intake around the 35th to 37th postmenstrual day, or a syndrome of anorectal stenosis, inguinal hernia, and triphalangy of the thumbs following ingestion of the drug around the 48th to 50th postmenstrual day. There is no overlap between these two phenotypes following very early and very late intake. If, however, cases with intake at various intervals in between, or cases with both early and late intake are studied, a clear pattern of the interconnected series of syndromes is seen.

The similarities and differences between thalidomide embryopathy and each of the seven genetic prototypes will now be discussed in more detail.

Prototype 1
Dominant Radius Aplasia

The main symptoms common in both dominant radius defects and thalidomide embryopathy are listed in Table III. There are no clear-cut signs present only in the dominant radius aplasia but lacking in thalidomide cases, though clinodactyly of the fifth fingers and mild funnel chest appear to be common in the genetic prototype but not in thalidomide cases. The difference between prototype 1 and its phenocopy may be in part explained in terms of the time sequence of organogenesis. The dominant gene appears to affect development only between the 42nd and 50th postmenstrual day. This may explain why ear defects and renal malformations are absent. But difference in time cannot explain everything. The defects of the lower limbs in thalidomide cases originate at the same time—around the 44th to 46th day—when thalidomide causes arm defects identical to those seen in the dominant radius defect syndrome. This may be explained by assuming that the same normal

<p>| TABLE III |</p>
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<thead>
<tr>
<th>Dominant Radius Defect</th>
<th>Thalidomide Embryopathy</th>
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<tbody>
<tr>
<td>Duane syndrome</td>
<td>+</td>
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<tr>
<td>Proximal defect of humerus</td>
<td>+</td>
</tr>
<tr>
<td>Radius hypoplasia</td>
<td>+</td>
</tr>
<tr>
<td>Radius aplasia</td>
<td>+</td>
</tr>
<tr>
<td>Radioulnar synostosis</td>
<td>+</td>
</tr>
<tr>
<td>Thumb hypoplasia</td>
<td>+</td>
</tr>
<tr>
<td>Thumb aplasia</td>
<td>+</td>
</tr>
<tr>
<td>Thumb triphalangy</td>
<td>+</td>
</tr>
<tr>
<td>Heart (arterial septal defect)</td>
<td>+</td>
</tr>
<tr>
<td>Heart (ventricular septal defect)</td>
<td>+</td>
</tr>
<tr>
<td>Midface haemangioma</td>
<td>+</td>
</tr>
<tr>
<td>Anotia</td>
<td>-</td>
</tr>
<tr>
<td>Amelia of arms</td>
<td>-</td>
</tr>
<tr>
<td>Duodenal atresia</td>
<td>-</td>
</tr>
<tr>
<td>Complex cardiovascular malformations</td>
<td>-</td>
</tr>
<tr>
<td>Kidney malformations</td>
<td>-</td>
</tr>
<tr>
<td>Femur defects</td>
<td>-</td>
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<tr>
<td>Tibia defects</td>
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</table>
embryological process is blocked to a lesser degree by the gene than it is in some instances by thalidomide. If thalidomide malformations are studied in relation to the amount of the drug ingested, it is apparent that leg malformations do not usually occur at doses less than 100 mg/day taken for more than one day. It is a well-known fact from experimental teratogenesis in mammals, that the hind legs are more resistant to teratogenic agents than the arms (von Kreybig, 1968).

One striking fact about the dominant prototype 1 is the variability of the phenotype. A mother with triphalangy or hypoplastic thumbs only and with no cardiac defect may have a child with severe three-finger phocomelia with distal humerus rudiments. A similar difference in thalidomide cases can be attributed to a time difference of about one week—50th versus 43rd postmenstrual day. It is difficult to understand how one and the same gene may have different times of activity in different patients.

The Duane syndrome has been reported in a few patients with prototype 1 (Mennerich, 1923; Gifford, 1926; Ferrell, Jones, and Lucas, 1966). The relative scarcity of reported cases of Holt–Oram syndrome showing this association may be misleading. The Duane syndrome may easily escape the attention of a physician mainly interested in the more conspicuous orthopaedic or cardiologic problems of his patients. Judging from the thalidomide experience the Duane syndrome has a still earlier origin at around the 35th to 37th postmenstrual day. The association of two such rare and not directly related conditions as radius defects and the Duane syndrome both in the genetic prototype 1 and in thalidomide embryopathy suggests a common biochemical pathway. The Duane syndrome can also occur alone as a dominant condition. The Duane syndrome within the framework of thalidomide intake is not a true phenocopy, as it is almost invariably associated with ear defects; an association apparently unknown as a genetic entity.

Both abducens and facial paralysis in thalidomide cases are usually interpreted as showing that thalidomide does not only affect mesodermal structures, such as muscles and bones, but also ectodermal structures (Partsch, 1969). I doubt whether this is justified, although thalidomide might interfere primarily with the development of the facial and eye muscles. The close proximity of the premyoblast cells from which the facial muscles originate to the origin of the external ear in the 4.2–6.5 mm embryo (Gasser, 1967) might explain the association of anotia and so-called cranial nerve defects in thalidomide embryopathy.

**Prototype 2**

**Radius Aplasia–Thrombocytopenia Syndrome**

Superficially, this syndrome with radius aplasia or phocomelia of the arms is strikingly similar to many cases of thalidomide embryopathy. The similarity extends to midfacial haemangioma, cardiovascular defects, and dislocation of the hip. There are, however, several clearly distinctive signs which have been found in every case of prototype 2 and in no case of thalidomide embryopathy. These are thrombocytopenia with deficiency of megakaryocytes in the bone marrow; neonatal leucocytosis; essentially normal thumbs, but with the radii invariably absent (see Fig. 3); and brachymesophalangy of the fifth fingers.

Ear defects, paralysis of cranial nerves, renal malformations, bone defects of the legs, and triphalangy of the thumbs do not occur in the radius aplasia–thrombocytopenia syndrome. The critical period of organogenesis which is affected in this syndrome would appear to be narrowly restricted to about the 44th to 45th postmenstrual day. The difference between the genetic prototype 2 and thalidomide embryopathy, however, cannot be explained by differences in time and/or by the degree of inter-

**FIG. 3.** X-ray typical of radius aplasia–thrombocytopenia syndrome in one of two affected sibs. (Orthopaedic Clinic, Huffer-Stiftung, Münster University.)
ference with normal organogenesis. There is an obvious qualitative difference: in prototype 2 a small misshaped rudiment may be all that is left of the three long bones of the arms, and yet the hand has five metacarpals and five fingers, whereas in thalidomide cases long bone defects of the arm of a similar degree are invariably accompanied by aplasia of other fingers as well. Differential diagnosis is unambiguous in every single cases of the radius aplasia–thrombocytopenia syndrome. Thus, even if the platelet deficiency is not considered, thalidomide does not produce a true phenocopy of prototype 2.

The skeletal phenotype of prototype 2 alone is sufficiently distinct to make the diagnosis virtually certain. Cases in which the platelets have not been studied but with the same pattern of bilateral radius aplasia and five fingers present probably should be included in the same category (Vrolik, 1849; Gruber, 1865; Rodenstein, 1875/76; Blencke, 1904; Homi, 1920; Hill, 1937; Birch-Jensen, 1949 [p. 104; Figs. 58 and 427]; Barsky, 1958; Gerold, 1959; Matzen und Fleissner, 1969 [Fig. 589]; G. Farkas, personal communication). These cases have never been found with dominant transmission. The distinction from dominant radius aplasia is clear cut both by phenotypical and genetic criteria. Two or more cases within one sibship have been reported by Blencke (1904), by Barsky (1958), and by Gerold (1959).

The genetics of the radius aplasia–thrombocytopenia syndrome is not quite clear. The incidence of the condition for autosomal recessive inheritance in sibs of probands agrees fairly well with expectation. Consanguinity of parents has not been noted so far. Formally, this absence of parental consanguinity in a rare familial condition, may be explained by postulating a compound heterozygote of two alleles $t_1$ and $t_2$ of the normal allele $t_0$. If homozygotes for $t_2$ were lethal in early embryonic life, the possibility of detecting them would be minimal. But what about the homozygotes for $t_1$? They might represent Fanconi’s panmyelopathy, which has thrombocytopenia, radial defects, and sometimes cardiac defects in common with the radius defect–thrombocytopenia syndrome. Alternatively, both homozygotes, $t_1t_1$ and $t_2t_2$, might be lethal and the compound, $t_1t_2$, might show imperfect intragenic complementation.

Prototype 3

Fanconi’s Panmyelopathy

Fanconi’s panmyelopathy can be associated with a surprising variety of malformations, most of which also occur in thalidomide cases (see Tables IV and V). The incidence of internal malformations in cases of Fanconi’s anaemia reported in the literature is heavily influenced by the fact that surviving cases are much more likely to be published. If the index cases are left aside, the very high incidence of gross malformations in stillborn sibs tends to give much higher estimates.

Most of these malformations, especially deafness and renal defects, correspond to the effect of the intake of small doses of thalidomide during the first half of the sensitive period of thalidomide embryopathy, ie, between the 35th and 42nd day; malformations phenocopied later, like triphalangy of the thumbs, are rare. While the pattern of organ malformations is very similar in Fanconi’s panmyelopathy and in thalidomide embryopathy, both conditions have additional distinctive symptoms, so that serious diagnostic doubts do not occur. Thrombocytopenia, leucopenia, and anaemia as well as pigment spots, dwarfism, and chromosome breaks typical of Fanconi’s panmyelopathy are not seen in thalidomide embryopathy. It does not necessarily follow that the basic mechanism is different in both conditions. The same biochemical mechanism might be permanently but incompletely blocked in the genetic prototype and intermittently in the

### Table IV

<table>
<thead>
<tr>
<th>Malformations Found in Fanconi’s Panmyelopathy (Batke, 1964)</th>
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<tbody>
<tr>
<td>Radius aplasia</td>
</tr>
<tr>
<td>Radius hypoplasia</td>
</tr>
<tr>
<td>Radioulnar synostosis</td>
</tr>
<tr>
<td>Thumb aplasia</td>
</tr>
<tr>
<td>Thumb hypoplasia</td>
</tr>
<tr>
<td>Thumb triphalangy (rare)</td>
</tr>
<tr>
<td>Pelvic dystopia of kidney</td>
</tr>
<tr>
<td>Hydronephrosis</td>
</tr>
<tr>
<td>Renal aplasia</td>
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<tr>
<td>Pelvic aplasia</td>
</tr>
<tr>
<td>Aplasia of internal ear</td>
</tr>
<tr>
<td>Malformed auricles</td>
</tr>
<tr>
<td>Deafness</td>
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</table>

### Table V

<table>
<thead>
<tr>
<th>Malformations Found in 133 Cases of Fanconi’s Panmyelopathy (Batke, 1964)</th>
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<tbody>
<tr>
<td>Radius</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>Aplasia</td>
</tr>
<tr>
<td>Hypoplasia</td>
</tr>
<tr>
<td>Radioulnar synostosis</td>
</tr>
<tr>
<td>Thumb</td>
</tr>
<tr>
<td>Aplasia</td>
</tr>
<tr>
<td>Hypoplasia</td>
</tr>
<tr>
<td>Unspecified defects</td>
</tr>
<tr>
<td>Duplication</td>
</tr>
</tbody>
</table>
Pharmacological phenocopy. Permanent high intake of thalidomide during the whole sensitive period seems to be invariably lethal in human as well as in some other primate embryos.

Thrombocytopenia has been a rather common side effect of thalidomide taken by adults. It has been attributed to drug allergy, but this has never been proved. The mechanism may be the same as in Fanconi's anaemia.

**Prototypes 4 and 5**

There is some doubt about the identity (J. Opitz, personal communication) or non-identity (McKusick, 1971) of type 4 (Roberts' syndrome [1919] of tetraphocomelia) and type 5 (the SC-pseudothalidomide syndrome). In Roberts' syndrome the limb defects are more severe, there is bilateral cleft lip and palate, and the face is definitely malformed with a flat nose and prominent eyes. There is no close similarity in any details to thalidomide cases. Bilateral cleft lip and palate do occur in thalidomide cases, though rarely, and then only in association with ear malformations.

In the pseudothalidomide syndrome only the arms may be malformed, while the legs remain normal, or the fibulae may be missing with the tibiae present and fused with the femora; this type of defect is unknown in thalidomide cases. Severe hypoplasia of the thumbs and the fifth fingers, presence of all fingers even with aplasia of radius and ulna, and synostosis of the fourth and fifth metacarpals are further characteristics of the pseudothalidomide syndrome. Thalidomide cases are not phenocopies of either syndrome, the morphological differences suggest different developmental mechanisms. In Roberts' syndrome (1919) and in the pseudothalidomide syndrome, however, the same basic mechanism may well be affected. If the differences do not represent variable manifestations of the same gene, they may be due to isoallelic mutations. Cases with intermediate morphology, such as the one reported by Ströer (1939)—cleft lip and palate, well developed humeri, aplasia of radius, ulna and fibula, synostosis of the fourth and fifth metacarpals, aplasia of thumbs—suggests that both conditions may only be the extreme manifestations of one entity. Alternatively, such intermediate cases may represent independent isoallelic mutations. For instance, in Ströer's case (1939) a compound heterozygote of the two isoallelic mutations underlying Roberts' syndrome (1943) and the pseudothalidomide syndrome is virtually excluded, because the parents were related. Ströer's assumption (1939), that cleft lip and palate without limb deformities when present in a few members of the same family, is a manifestation of the heterozygote state, receives at best weak support from his published pedigree and none from other reports.

**Prototype 6**

**Tibia Aplasia with Triphalangy of Thumbs**

Bilateral aplasia or severe hypoplasia of the tibia in association with excessive preaxial polydactyly of the feet and triphalangeal thumbs has been observed with a clearly autosomal dominant pattern of transmission (Eaton and McKusick, 1969). In some members only triphalangy of the thumbs with preaxial polydactyly of the hands (Lenz, Theopold, and Thomas, 1964, one unpublished observation) or triphalangy of the thumbs only (Reber, 1967/68) is seen.

Reber also found a case of postaxial hexadactyly of both hands in a distant relative, related to the patient through seven unaffected persons. There is no good reason for his assumption that this case has the same genetic basis as preaxial polydactyly in father and son.

Tibia aplasia with duplication of the big toes and triphalangeal thumbs also occurs following thalidomide intake between the 46th and 50th postmenstrual day (see Figs. 4a and 4b). In the genetic prototype the triphalangeal thumbs are rather well developed, preaxial polydactyly of the hands is more common, and the polydactyly of the feet may be excessive—eight toes on either foot. Polydactylism with postminimus of the hands is only seen in some cases of the genetic syndrome.

The analogy between genetic prototype and phenocopy is so close that it is difficult to escape the conclusion that the same mechanism is affected. The existing differences may be due to differences in time and degree of the block. The tibia aplasia—triphalangey syndrome seems to represent a block acting during a shorter period, than in the Holt–Oram syndrome.

**Prototype 7**

**Triphalangeal Thumbs with and without Preaxial Polydactyly**

Triphalangeal thumbs which sometimes look very much like index fingers can occur in the Holt–Oram syndrome, in the tibia aplasia–triphalangey syndrome, and, though rarely, in Fanconi's pannmyelopathy. Triphalangy of the thumbs with congenital anaemia and with a ventricular septal defect in one case, as seen by Aase and Smith (1969) in two brothers, may be a separate entity. In families with typical Holt–Oram syndrome some members may show triphalangeal thumbs as the only abnormality. It is
Figs. 4a and 4b. Thalidomide embryopathy. Irregular intake of thalidomide before and during early pregnancy.
FIG. 5a and 5b. Thalidomide embryopathy: triphalangy and polydactyly. The first of several prescriptions of thalidomide was probably taken on the eighth postmenstrual day if the average duration of pregnancy is assumed.

Fig. 6. Thalidomide embryopathy. Thalidomide was prescribed during the second month of pregnancy. The right hand is an almost exact mirror image of the left hand.
Figs. 7a and b. Dominant triphalangeal thumbs with preaxial polydactyly.
difficult, therefore, to decide whether in a given family with few affected members triphalangy of the thumbs is a phenotypical variety of the Holt–Oram syndrome, or an independent entity. In some families, triphalangy of the thumbs with or without concomitant cardiac malformations is seen in some members, whereas aplasia of the thumbs and radio-ulnar synostosis is seen in others (Haas, 1939; Ferber, 1953). These cases probably belong to the Holt-Oram syndrome, and they may show the mesobrachyphalangy of the fifth fingers and funnel chest often found in that condition. In other families triphalangy is associated with duplication and even triplication of the thumbs. Nylander (1931) observed duplication of the thumbs and higher degrees of preaxial polydactylism, up to five thumbs, usually combined with triphalangy in 41 members of a large Swedish kinship. Müller (1936) reported a family with 11 members in three generations affected by triphalangeal thumbs and preaxial polydactyly.

In some families, triphalangeal thumbs are associated with preaxial polydactyly of the hands and feet (Atwood and Pond, 1917; Manoiloff, 1931; Haas, 1939; Hefner, 1940; Barsky, 1951; Komai, Ozaki, and Inokuma, 1953; Hopf, 1959; Demarinis and Wildervanck, 1960; Kersting, 1966 [case 8]; Temtamy, 1966 [Fig. 7]). Another dominant type is triphalangy with doubling of the terminal phalanges of the thumbs (Lapidus, Guidotti, and Coletti, 1943; Ecke, 1962). Swanson and Brown (1962) observed duplication of the first phalanx in three out of 30 members of a family with bilateral triphalangeal thumbs. Two out of four members affected with triphalangy in a family reported by Müller (1937) had duplicated thumbs as well. Wildervanck (1954) saw additional trapezoid shaped middle phalanges of the thumbs in six members in three generations of a family. Unilateral duplication of the terminal phalanx was present in one case. In a family reported by Ströer (1936) 16 patients in five generations had triphalangeal thumbs, preaxial polydactyly and complete syndactyly of the third to fifth fingers or fourth and fifth fingers bilaterally.

**Fig. 8a.** Triphalangeal thumbs. Autosomal dominant type. There are six cases in two generations of this family.

**Fig. 8b.** The same anomaly in a second cousin of the patient shown in Fig. 8a. (Institute of Human Genetics, Münster University.)
In still other families triphalangeal thumbs are inherited as an isolated autosomal dominant trait with a more regular manifestation than is usually found in Holt–Oram families (Salzer, 1898; Roberts, 1943; Sallam, 1955; Klemm, 1956; Barsky, 1958; Abramowitz, 1959; Frere, 1960; Kersting, 1966 [case 5; see Fig. 8]). Rudimentary postaxial polydactyly is occasionally seen in members of families with this later type of application, in which preaxial polydactyly is rare (Rieder, 1900; Cotte, 1923).

Triphalangy of the thumbs in thalidomide cases is variable. It is sometimes associated with polydactyly of the hands or feet (see Figs. 6 and 9). But judging from the thalidomide experience the dominant types of triphalangeal thumbs represent a genetic block strictly limited in time to the end of the sensitive period of organ development.

Varus angulation of the femur, similar to that seen in some late-intake thalidomide cases in association with triphalangeal thumbs and occasionally in the radius aplasia—thrombocytopenia syndrome, has been described by Polinelli (1962) in one affected member of a family with six cases of triphalangy of the thumbs in four generations—where one case was associated with preaxial polydactyly of the hands.

One might, of course, attempt to split triphalangy of the thumbs into still more types. It is not quite clear, however, how they should be delineated. While in a given family the morphological type tends to be generally the same and different from that seen in many other families with triphalangy, there is some intrafamilial variability and some overlap between types.

One might, furthermore, enlarge the list of prototypes of thalidomide embryopathy by adding: (1) the autosomal recessive poikiloderma–radius aplasia syndrome; (2) isolated preaxial polydactyly of the feet, or (3) the dominant isolated radioulnar synostosis, which is very much like the same abnormality seen in thalidomide cases. In thalidomide embryopathy, however, skin changes are absent, preaxial polydactyly of the feet does not

![Fig. 9. Thalidomide embryopathy. Two tablets of thalidomide were taken on the 45th postmenstrual day.](image-url)
occur without hand malformations, and radioulnar synostosis is always associated with aplasia or hypoplasia of the radial ray.

**Summary of Comparisons of Thalidomide Phenocopy with Genetic Prototypes**

Thalidomide embryopathy comprises a great variety of skeletal and other malformations, many of which are also seen in genetic disorders, sometimes in the same characteristic patterns. Many cases of thalidomide embryopathy closely mimic genetic malformations. They are probably true phenocopies. However, the concept 'phenocopy' does not adequately describe the total phenotypical spectrum of thalidomide embryopathy, which comprises many complex malformation patterns for which a genetic prototype is unknown. The monogenic prototypes differ from thalidomide embryopathy in several ways.

1. There is less variability in degree.
2. There is less variability in the timing of the block interfering with embryonic development.
3. Some genetic prototypes show symptoms unknown in thalidomide embryopathy. This difference probably reflects either different basic mechanisms (probably for types 4 and 5), or the consequences of a permanent partial block in the genetic prototype, as compared to an intermittent block in thalidomide embryopathy.
4. Thalidomide cases do show some malformations not seen in the genetic prototypes. This may be due to temporary complete blocking of a metabolic pathway, the permanent genetic blocking of which would be lethal.
5. Some genetic prototypes predominantly show malformations corresponding to a block in the first half of the sensitive period (prototype 3), others predominantly to a block in the middle period (prototypes 1 and 2), still others to a late block (prototypes 6 and 7).

**Speculations on the Nature of the Thalidomide Block**

Nudleman and Travill (1971) have produced defects of the preaxial structures of the upper limbs in rabbits by feeding thalidomide to the females on days 7–11 of pregnancy. The fetuses were removed on day 21. The most striking difference between experimental and control animals was seen in the glycogen content of hypertrophic chondrocytes and calcified chondrocytes, which were depleted of glycogen in the controls and filled in the thalidomide-treated animals. A similar interference with glycogen utilization was seen in the hypertrophic chondrocytes of the sternebrae of thalidomide-treated rats (Globus and Gibson, 1968). These experimental findings fit in with the speculation that thalidomide might interfere with mobilization of embryonic glycogen, based on the correspondence between the distribution of embryonic glycogen in the embryo and the pattern of thalidomide malformations (Lenz, 1963). Dyban (1962) has studied the glycogen content of different tissues in human embryos and collated the data with similar studies from other mammals. Accumulation typically precedes morphological differentiation of the blastemas, from which the heart and the gut, the auditory canal, the muscles, and the skeleton originate. This is not the case, or only to a lesser extent in the precursor cells of the liver, the spleen, the gonads, and the central nervous system. Embryonic glycogen appears to be different from adult glycogen. It is more resistant to histochemical procedures. If the teratogenic action of thalidomide is explained by interference with glycogen mobilization, it becomes necessary to postulate different metabolic pathways for embryonic and adult glycogen, because the well-known postnatal glycogenoses are not associated with gross morphological malformations.

The genetic prototypes of thalidomide embryopathy lend themselves to speculations along the same lines. Thalidomide may be conceived of as an inhibitor of an enzyme engaged in the mobilization of embryonic glycogen. The genetic prototypes would then possibly affect the same metabolic chain at the same or at adjacent links.

**References**


Phenocopies


Phenocopies.

W Lenz

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