THE EMBRYONIC DEVELOPMENT OF MUTANTS OF THE *Sd*-STRAIN IN MICE[1]

S. GLUECKSOHN-SCHOENHEIMER
Department of Zoology, Columbia University

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A SYNDROME of abnormalities in the mouse has been described (GLUECKSOHN-SCHOENHEIMER 1943) in which defects in the spinal column, the urogenital system, and the intestine are associated together in animals which are heterozygous or homozygous for a single mutation, *Sd* (DUNN, GLUECKSOHN-SCHOENHEIMER, and BRYSON 1940). These defects—as apparent in the mutant mice between birth and adult life—consist in reduction or absence of the tail, spina bifida, and vertebral abnormalities, while reduction or absence of kidneys, presence of a cloaca, absence of rectum and imperforate anus are the abnormalities found in the urogenital system and the intestine. The homozygotes, which are always grossly defective, die shortly after birth, while heterozygotes may suffer a high mortality in early life.

The abnormalities as found in these newborn and adult mice represent the end result of a chain of events at the beginning of which stands the gene. The analysis of the action of the gene is our ultimate goal; at the present, however, we must content ourselves with the description of as many visible effects as possible of the chain of processes started by the gene. Beginning with the end result—that is, the malformations in the newborn—we trace back the developmental history of the abnormal organs throughout embryogeny until we come to a stage where morphological methods are not sufficient to distinguish the abnormal from the normal. A further analysis of the processes bringing us closer to the gene must be left to experimental rather than descriptive methods.

The present paper deals with the embryonic development of the abnormal organ systems in heterozygous and homozygous *Sd* mice. The organs affected are the spine, the urogenital system, and the intestine. We know of several other mutations producing malformations in the sacral and caudal parts of the spine; the processes which in the different mutants lead to the same end results (for example, tail-shortening, fusion and abnormalities of individual vertebrae) will be compared with each other.

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MATERIAL AND METHODS

The material for the embryological investigations was obtained from matings of heterozygous animals (*Sd* +) *inter se* and from outcrosses of heterozygotes to normals. The embryos were timed and obtained by the methods described previously (GLUECKSOHN-SCHOENHEIMER 1938).

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Embryos were studied between the ages of eight days and 17 days after fertilization. Sixty-two litters were dissected, and a total of 576 embryos was obtained. Of these, heterozygous (*Sd* +) embryos up to and including the 11th day after fertilization could not be diagnosed with absolute certainty as to their genotype in regard to *Sd*. The distribution of 241 embryos of 12 days and older among the different classes obtained from crosses of *Sd* + to normal and to *Sd* + was as follows: (1) from crosses of *Sd* + by ++:88 *Sd*+ 86++; (2) from crosses of *Sd* + by *Sd* +:20 ++ 29 *Sd* + 18 *Sd Sd*, the departure from the expected ratio of 1:2:1 not being significant.

All embryos were fixed in Bouin, imbedded in paraffine, sectioned at 8μ, and stained in Delafield's haematoxylin and eosin.

DEVELOPMENT OF THE HETEROZYGOUS SHORT-TAILED OR TAILLESS EMBRYOS (*Sd* +)

Tail

The development of the prospective short-tailed or tailless heterozygous embryos progresses normally up to the tenth day. At the age of about 10½–11 days differences between normals and heterozygotes become apparent externally, the heterozygotes showing slight abnormalities. The last few somites of the tail may appear small and irregular, and small haematomata are found in the posterior part of the tail. The tail somites degenerate progressively, starting distally and proceeding in proximal direction. A gradual decrease in the diameter of the tail may be observed, the more distal portions shrinking rapidly and the shrinking progressing proximally. Extravasation of blood in distal portions of the tail appears in the early degenerative stages (ten days); the haemorrhages increase in size and may sometimes fill one third to one half of the entire tail (fig. 1). No sharp point of constriction between normal and abnormal part of the tail, as described for the Brachyury mutation (CHESLEY 1935), can be found in the *Sd* + embryos, but the tail becomes thinner gradually. The distal abnormal portion of the tail may persist as a filament throughout the life of the abnormal mouse.

Histologically, abnormalities in the tail of the heterozygotes may be observed slightly before they become apparent externally. The distal somites of the tail at the age of ten days contain pycnotic granules; these granules can also be found in the mesenchyme between and around the somites and in the neural tube. Simultaneously, the small haemorrhages containing blood extruded from the vessels appear in the distal part of the tail. But cell pycnosis was observed also in the absence of haematomata. The number of pycnotic granules and the size of the blood extravasations increase as development proceeds and the distal somites appear now small and irregular. Eventually, all structures in the affected part of the tail break down, such as neural tube, notochord, tail gut and blood vessels (fig. 3, 4). The degeneration of all these structures sets in simultaneously at the age of 11 days and is a secondary process following the process of cell necrosis in the neural tube, somites and mesenchyme, and the appearance of extravasated blood.

Notochord and intervertebral discs

The entire notochord of the embryo degenerates subsequent to the appearance of abnormal processes in the tail. In sections of embryos of the 11th day the notochord appears discontinuous; it breaks up and eventually disappears throughout the length of the animal, leaving behind only scattered remnants consisting of two or three abnormal cells each. As a result of the disintegration of the notochord, a normal nucleus pulposus fails to appear. The significance of the absence of the notochordal remnant during the development of the intervertebral disc remains unknown. Apparently, the development of the intervertebral disc is not greatly disturbed by the absence of the nucleus pulposus, because no abnormalities other than an occasional lordosis, kyphosis, or scoliosis or occasional fusions of individual vertebrae were observed in the spine of adults. Since the notochord and thus the nucleus pulposus is abnormal at all levels of the spine, the normal development and function of any intervertebral disc would indicate that the nucleus pulposus is not an essential part of the intervertebral disc.

Sacral region

No gross abnormalities were observed in the sacral region of the heterozygous embryos; the development of the vertebrae from the somites was not studied in detail.

Urinary organs

In view of the variety of abnormalities of the urogenital system in the adult (GLUECKSOHN-SCHOENHEIMER 1943), corresponding variations of developmental abnormalities in the embryo are to be expected. The development of the urogenital system of *Sd* heterozygotes is normal up to the time when the ureters bud off from the mesonephric ducts. The first abnormalities were found in embryos at the age of ten days; one embryo which on the basis of tail abnormalities had been classified as *Sd* + had a short, round and broad ureteric bud instead of the narrow long bud with the widened distal end (that is, the primitive renal pelvis) found normally. Another embryo from the same litter showed duplication of ureteric buds, the secondary bud coming off from the mesonephric duct slightly posterior to the primary bud. This duplication of ureteric buds is a frequent occurrence in the heterozygotes (fig. 7). The secondary bud is always shorter than the primary one; it does not connect with the metanephros and does not become functional; this finding agrees with the fact that double ureters were never found in adult heterozygotes.

At the age of 11 days after fertilization the widened distal end of the normal ureter—that is, the primitive renal pelvis—begins to branch and the cranial and caudal pole tubules are formed (fig. 6). The metanephrogenic tissue which is located around the ureter tip forms little caps around the tips of both the cranial and the caudal pole tubule. The caudal and cranial pole tubules divide again, each branch carrying the cap of metanephrogenic tissue around its tip. The pole tubules develop into the collecting tubules—that is, the excretory system of the kidney—and the caps of metanephrogenic tissue form the secretory elements—namely, the secretory tubules and renal corpuscles.

In the heterozygous mutants (*Sd* +) the development of this system of tubules is inhibited entirely or disturbed. In the case of complete inhibition, the distal end of the ureter (the primitive renal pelvis) does not branch at all and no tubules develop (fig. 7). In other cases, the inhibition is not complete and the branching of the ureter tip proceeds to a certain extent, more slowly than in the normal and resulting in a smaller number of tubules. Once the process of branching is initiated, each tubule develops normally into an excretory element, with the metanephrogenic tissue covering its tip and finally differentiating into the secretory tubules and renal corpuscles. Of the two systems of the metanephros, the secretory and excretory, the secretory part of the metanephros never develops in the absence of the excretory part, in spite of the presence of the metanephrogenic tissue in all heterozygotes. Its formative development does not take place unless it is preceded by the formation of the excretory system from the distal end of the ureter. If the ureter is missing completely or if its distal end does not branch at all, absence of the kidney will result from it; in case branching does take place, the size of the kidney will depend on the extent of the branching process and the number of tubules resulting from it.

DEVELOPMENT OF THE HOMOZYGOUS EMBRYOS (*Sd Sd*)

Tail

The homozygous *Sd Sd* embryo can be distinguished from its normal and heterozygous litter mates at the end of nine days after fertilization by macroscopic examination. At that stage, the tail bud begins to elongate in both the normal and the homozygote, but in the homozygote a constriction appears at the tail base. The constricted tail is shorter and thinner than the normal tail. It is characterized by haematomata of different sizes in its distal part. These haematomata can be seen on macroscopic examination. In sections of the tail bud at nine days all structures of the tail are clearly abnormal: the notochord does not appear as a continuous rod, but only traces of it are found, while in earlier stages it appears perfectly normal; the neural tube extends into the tail as does the tail gut, and somites are present. All these tail structures contain large numbers of pycnotic granules. These can be found in the neural tube, around the somites, inside the somites, and all through the tail mesenchyme (fig. 5). The number of pycnotic granules increases as the degenerative processes in the tail continue; the haematomata become bigger due to the addition of more blood extruded from the blood vessels; eventually all the structures break down, and at the end of 12 days only a filament is left with one or several large haematomata inside which are gradually resorbed. Due to the haematomata the tail appears swollen in spots and shows alternating bulges and constrictions (fig. 2).

Sacral region

The sacral region of the *Sd* homozygotes is characterized by the failure of the neural folds to close; a cleft is visible between the neural folds covered by a large transparent bleb of the epidermis. This embryonic abnormality is directly connected with one of the malformations regularly encountered in the

newborn *Sd* homozygotes—that is, spina bifida (GLUECKSOHN-SCHOENHEIMER 1943). Another characteristic external feature of the *Sd* homozygotes at the age of 11 and 12 days after fertilization is the failure of development of the genital papilla which in the normal embryo first appears at this age and grows during the succeeding days. Thus, by the age of 11 days the homozygous *Sd* embryo is easily recognized externally by the abnormal appearance of the tail, by the absence of the genital papilla, and by the large bleb above the cleft neural folds in the sacral region.

Urogenital System of the Homozygotes

The abnormalities in the developing urogenital system of the homozygotes are more extensive than those described for the heterozygotes just as the urogenital malformations in the homozygous newborn are more extensive than those of the heterozygotes. At the end of nine days or the beginning of ten days after fertilization the mesonephric ducts are frequently abnormal in their posterior portion; they do not reach beyond the point where the ureter bud comes off and do not establish a connection with the cloaca. This posterior part of the mesonephric duct is normally taken up into the bladder, and the abnormalities of the bladder described for the homozygous newborns (complete absence or abnormally small size) may well be connected partly with the failure of the posterior part of the mesonephric duct to develop. The completely normal appearance of the gonads and their ducts, on the other hand, shows that the mesonephros and the anterior part of the mesonephric duct which are normal morphologically are normal in their developmental potencies as well.

The ureters bud off from the mesonephric duct normally; but in most cases two buds come off from each mesonephric duct. This duplication of ureteric buds is more frequent than in the heterozygotes and is almost a regular feature of the homozygotes. Both primary and secondary ureters are underdeveloped, one usually more than the other; both stay short, turn dorsad and caudad, and usually the tips do not branch at all; occasionally cranial and caudal pole tubules develop, and even more rarely a few secondary tubules appear (fig. 8). Nephrogenic tissue is found around the tip of the ureter, but it fails to undergo any further differentiation, except for the rare cases in which some differentiation of the ureteric tip (=renal pelvis) occurs. The rather infrequent appearance of a very small solitary kidney in the newborn homozygotes reported before is linked up with the occasional slight differentiation of the ureteric bud.

The cloaca is abnormally small in the *Sd* homozygotes of about ten days. It does not grow normally, and its separation into urogenital sinus and rectum fails to take place. Occasionally, the vesical portion of the urogenital sinus develops to a certain extent, and thus can be explained the few cases of newborns which do contain a bladder, however small. The absence of the bladder in most cases and the failure of the rectum to develop thus go back to abnormalities of the cloaca in embryos of 11 and 12 days. The absence of genital papilla and anal opening are probably direct results of the absence of bladder and urethra and of the rectum.

DISCUSSION

In the development of the *Sd* mutants, both heterozygotes and homozygotes, two organ systems are affected, the axial skeleton and the urogenital system. As to the axial skeleton, it seems from the purely morphological evidence that the abnormal process affecting the tail in embryos of the *Sd* mutants differs from the abnormal processes which have been described for other tail mutants. The embryonic development of tail mutants has been investigated for the following mutations: flexed (*fl*), Brachyury short tail (*T*), and the two recessives t^0 and t^1. KAMENOFF (1935) showed that the presence of the flexes or fusions between contiguous vertebrae in the tails of adult flexed mice can be traced back to abnormalities in the intervertebral discs of flexed embryos: part of the cartilage of the intervertebral discs fails to differentiate into fibers. Although abnormal bending and branching of the notochord was observed in some of the flexed embryos, these abnormalities have no causal relation to the fusions of the vertebrae. No degenerative changes were observed in the tail region of flexed embryos.

A study of the development of mice carrying *T* alone (short-tailed mice) or *T* and t^0 or t^1 (tailless mice), showed that the notochord is the organ primarily affected in these mutants (CHESLEY 1935; GLUECKSOHN-SCHOENHEIMER 1938). In embryos of these mice the tail is at first formed normally from the tail bud; at the 11th day of development, however, a constriction sets in somewhere along the tail in the short-tailed mice ($T/+$) and at the tail base in the tailless mice (T/t^0 or T/t^1) which results in a resorption of the tail distal to the constriction. The absence of the tail and the abnormalities of the neural tube, somites, and other structures in the constricted part of the tail are secondary and can be traced back to the original abnormalities of the notochord.

The morphological picture produced in the posterior trunk and tail region of the *Sd* mutants indicates the presence of abnormal processes different from those in flexed, Brachury, and tailless mice. In *Sd* a cellular degeneration proc-

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EXPLANATION OF FIGURES

FIG. 1.—*Sd*/+ embryo. 12 days. Note haematoma in distal part of abnormal tail. ×9.

FIG. 2.—*Sd/Sd* embryo. same age. Note abnormal tail and absence of genital papilla. ×11

FIG. 3.—Sagittal section of tail of normal embryo 551, 2 r. 11 days. Note neural tube, notochord, somites, tail gut ×80.

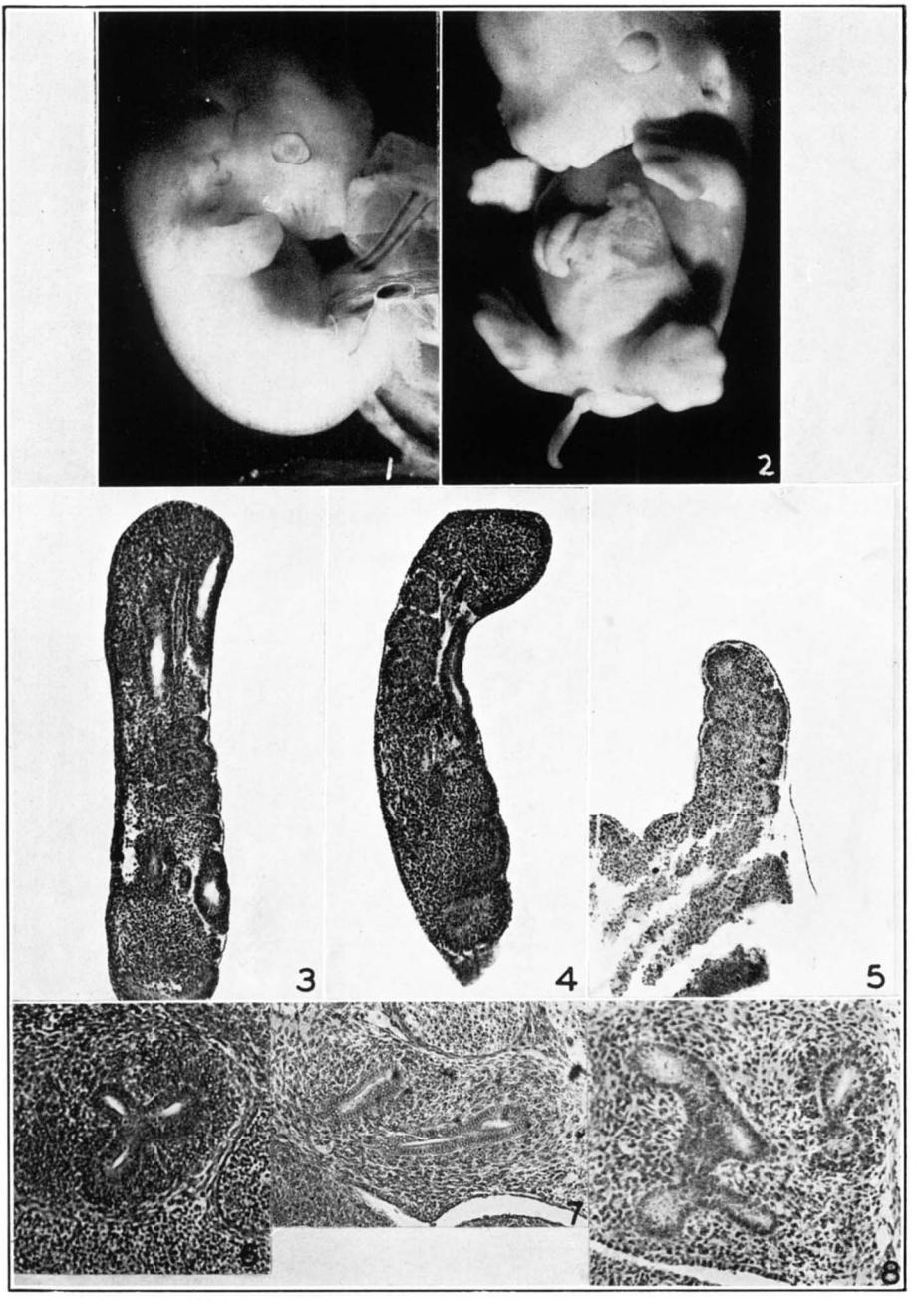
FIG. 4.—Sagittal section of tail of *Sd*/+ embryo. 551, 1 r. littermate of 551, 2 r. Note shrinkage of neural tube, breaking up of notochord, pycnotic granules in somites.

FIG. 5.—Sagittal section of tail of *Sd/Sd* embryo. 551, 3 r. littermate of 551, 2 r. Note somites and large number of pycnotic granules all through the tail. ×80.

FIG. 6.—Sagittal section through ureter tip of normal embryo. 5403, 2 r. 12 days. Note branching of tip into pole tubules and darkly stained metanephrogenic tissue around tubules. ×150.

FIG. 7.—Sagittal section through tips of double ureter of *Sd*/+ embryo, 5403, 5 r. littermate of 5403, 2 r. Note complete absence of branching in both primary and secondary ureter. ×150.

FIG. 8.—Sagittal section through urinary system of an *Sd/Sd* embryo, 6116, 1 l. 12 days. Below left, blind ending of mesonephric duct; primary and secondary ureter branching off to the right; lower ureter ends blindly, upper ureter branches once, both pole tubules carrying caps of nephrogenic tissue. ×150.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ess takes place in the mesenchyme of the tail with ensuing haemorrhages throughout the tail; subsequently degenerative symptoms in notochord, neural tube, and somites appear. Chromophilic granules, as symptoms of cell pycnosis, were also observed by CHESLEY (1935) in the posterior region of homozygous T/T embryos; however, this condition was not found to antedate other abnormalities. CHESLEY observed the same granules in T heterozygotes. But no cell degeneration as regular and as extensive as that in the *Sd* mutants was found in either short-tailed (T +) or tailless ($T\ t^0$ or $T\ t^1$) mice.

The appearance of haematomata in the abnormal tail seems to be due to a defect of the walls of the blood vessels rather than to any circulatory disturbance. Although abnormalities in the walls were not observed directly, their presence seems very likely, since cell degeneration was observed in all of the other tail structures. If, on the other hand, general circulatory defects were responsible for the breakdown of the tail vessels, one should expect haematomata to appear in the extremities as well, and this was not the case. The breakdown of the blood vessels in the tail does not seem to present an explanation for the abnormal processes in the tail because of the cases in which cell pycnosis was observed in the tail in the absence of haematomata.

A comparison of *Sd* embryos with flexed embryos shows that both mutants have abnormalities of the intervertebral discs, but those in the flexed mice are located in the fibrous part of the disc while in *Sd* mutants the nucleus pulposus (that is, the remnant of the notochord) is abnormal or missing.

Thus, the same end result—namely, abnormalities in the spine and tail—is achieved by different means in the case of these different mutations. This conclusion would not have been possible on the basis of studies of newborn and adult mutants alone. The abnormalities had to be traced back into embryogeny in order to find out the nature of the abnormal processes leading to the malformations. Thus, a fundamental difference appears between the actions of the different tail mutations which at first sight—that is, in the newborn and the adult—looked so very similar. Their similarity consists solely in affecting identical parts of the body, but the chain of events between the gene and the end organ is different in the case of each of these different mutations.

Only one other mutation in mice affecting the urogenital system has been described (BAGG 1925); it brought about absence or underdevelopment and pathological changes of one or both kidneys. Both the pathological anatomy of the abnormal kidneys in newborn and adults as well as the embryogeny of the abnormal organ systems of the BAGG abnormal mice (BROWN 1931) differ from those in the *Sd* mutants. The kidneys of the *Sd* mice differ from normal kidneys mainly in the number of elements; those elements that are present seem normal, while BAGG'S abnormal mice showed definite structural abnormalities of the elements of the kidney.

Our material seems to indicate that it is the ureter which is primarily affected by *Sd* and that the failure of its upper part (the primitive renal pelvis) to differentiate and branch properly, and thus to give rise to a normal excretory system, is responsible for the failure of the secretory system of the kidney to develop normally. Metanephric differentiation was never observed

in the absence of development of the renal pelvis. Differentiation of pole tubules from the primitive renal pelvis on the other hand was always accompanied by corresponding formation of secretory elements in the metanephrogenic tissue. Sometimes the ureter failed to branch off from the mesonephric duct altogether, in which case no metanephric development whatever occurred in spite of the presence of the metanephrogenic tissue. All these facts seem to justify the conclusion that the effect on the ureter precedes that on the metanephros proper. Since no earlier morphological abnormalities were found in the urogenital system of the *Sd* + or *Sd Sd* embryos, it is impossible to state which abnormal processes precede the abnormalities of the ureter.

The simultaneous effect of *Sd* on the axial skeleton and the urogenital system is a phenomenon which cannot be easily explained at the moment. Morphologically and embryologically, the organ systems affected have several properties in common: they are both located in the same region of the body—namely, the posterior region—and they are both of mesodermal origin. But an explanation of the simultaneous effect of the mutation *Sd* based on the common location of the organs concerned would seem doubtful, because other organs in that same region are not affected. The same argument would hold against an explanation based on the common mesodermal origin of axial skeleton and urogenital system since other mesodermal organs are not affected. It seems that in the absence of any knowledge about the primary action of *Sd* and about the normal primary processes in the early development of both axial skeleton and urogenital system, the problem of the pleiotropic effect of *Sd* has to be left open.

Recently, GRÜNEBERG (1943) formulated "two principles and five working postulates as a guide for the developmental analysis of morphological gene effects." The first principle excludes the existence of genuine pleiotropism, a viewpoint which GRÜNEBERG has held and discussed before. GRÜNEBERG'S second principle excludes the existence of organ-specific primary gene effects and asserts that the primary action of a gene is either cell-specific or tissue-specific. As GRÜNEBERG argues rightly, it is quite true that our present knowledge permits us to exclude the organ-specific action of genes, since organs represent such composite systems in their chemistry and metabolism that any primary action of the gene on an entire organ may be excluded from consideration. However, we may argue with equal justification against the concept of cell- and tissue-specific action of genes. Cells and tissues represent systems as composite in their chemistry and metabolism as do organs, and genes will not act on them primarily any more than they would on organs. According to our present idea of the action of genes, genes do not act directly on structural elements whether they be organs, tissues or cells, but their primary action concerns physiological processes—that is, not static but dynamic events are affected by them. It seems irrelevant for the problem of primary gene action whether the locus of expression of some particular gene action be cells, tissues, or organs.

We are not any more justified in drawing conclusions from the final result of gene action and calling the gene's primary action cell- or tissue-specific than

we are in calling it organ-specific. In each case, the eventual manner and place of expression of the gene action on morphological structure is far removed from its primary effect. This we can only visualize as affecting fundamental processes which underlie the formation of structure. A distinction between cell- and tissue-specific primary action on the one hand and organ-specific action on the other does not seem justified by the facts of embryology, genetics, or developmental genetics. We know of the interdependence of all parts of the organism during embryogeny, and of the state of flux of the embryo during development; due to this interdependence the process or processes singled out and acted upon by any one gene might find expression in cells or in tissues or in organs or in two or three of them simultaneously. Generalizations such as GRÜNEBERG's on the basis of his results (rat-lethal, mouse-hydrocephalus) do not seem to be justified. In his particular cases primary gene action might express itself in tissue-specificity (cartilage), but that does not mean that the primary action of the gene in question is tissue-specific or that gene action always is cell- or tissue-specific. The primary action of a gene is probably much more pervasive than is apparent from the gene's visible effects as observed with the crude morphological methods at our disposal. It is to be expected that new and different methods of study will reveal effects of genes overlooked in the first analysis. Furthermore, the eventual effect of a particular gene must depend not only on its own primary action but also on the reactivity of the different parts of the developing embryo and on the particular time at which the gene action takes place. Thus, if the action of a gene expresses itself in abnormalities of one particular tissue, it is conceivable that this tissue at the time was more sensitive to the action of the gene than any other tissue. In such a case one could not call the primary *action* of a gene tissue-specific although its *expression* is tissue-specific. The same argument holds for organs and cells. As to GRÜNEBERG's concept of pleiotropism—expressed in his first principle which excludes its existence—this has been discussed recently by DOBZHANSKY and HOLZ (1943) who rightly assert the futility of arguing about existence or non-existence of genuine pleiotropism as long as we do not know anything about the primary action of genes.

In our own case, cell- or tissue-specific action of the gene *Sd* are excluded on an equal basis with organ-specific action. The abnormalities of the skeleton and the urogenital system in heterozygous and homozygous *Sd* mice could not be traced back to any common primary tissue- or cell-abnormality. If any common abnormality exists, it must be looked for in some physiological process rather than in a morphological structure. Although no morphological abnormality was found prior to the specific abnormalities of the axial skeleton and urogenital system, it is highly likely that physiological abnormalities do exist before they become manifest morphologically. Before their nature is known it is not possible to decide whether or not these physiological abnormalities are responsible for both the skeletal and the urogenital abnormalities. Although a common morphological basis for the skeletal and urogenital abnormalities can thus be excluded, the question of the pleiotropic action of the *Sd* gene must be left unanswered.

SUMMARY

The development of embryos heterozygous and homozygous for the dominant mutation *Sd* is described.

Two organ systems are affected in these mutants: the axial skeleton and the urogenital system.

The tail of the heterozygotes shows the first abnormalities at the end of ten days after fertilization: cellular degeneration products and small haematomata appear; eventually, the abnormal part of the tail is resorbed.

The tail of the homozygotes shows the first abnormalities at the end of nine days. Again, cellular degeneration products and haematomata are typical symptoms and eventually the entire tail is resorbed.

In both heterozygotes and homozygotes abnormalities of the notochord and neural tube are secondary to the cell degeneration processes in the tail.

The processes leading to the abnormalities of the tail in *Sd* mice differ from those in other known tail mutants.

The urogenital abnormalities of the heterozygotes appear at the age of ten days and consist in that stage in abnormalities of the ureter followed later by abnormalities of the metanephros.

The homozygous embryos show the first urogenital abnormalities around the beginning of ten days after fertilization; the posterior part of the mesonephric duct is missing in most cases, the ureters are short and displaced and frequently doubled. Normal metanephric development never occurs.

From the study of the development of urogenital malformations in heterozygotes and homozygotes it is concluded that the metanephric abnormalities are dependent on those of the ureters.

The problem of the simultaneous effect of *Sd* on axial skeleton and urogenital system is discussed from the developmental point of view.

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