The glandular aspects of the tabby syndrome in the mouse

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This paper is dedicated in gratitude and affection to Professor Hans Nachtsheim on the occasion of his 80th birthday on 13 June 1970

SUMMARY

The tabby syndrome includes abnormalities of the coat and of the sinus hairs, of the teeth, of a multitude of exocrine glands and of some surface structures like tail rings, plicae digitales and the papilla vallata of the tongue. All structures known to be affected by the tabby gene arise by the downgrowth of a surface epithelium into the membrana propria. The involvement of some structures but not of others cannot be accounted for by common origin from one germ layer (as both ectodermal and endodermal derivatives are involved), nor by common function of the structures affected, nor by a time concept such that structures formed before a critical period escape unharmed. The fault may lie either with the surface epithelium, or with the stimuli from the membrana propria which elicit local downgrowth, or with the interaction between the two. It seems least likely that the fault lies with the membrana propria, but a decision cannot be made on the information so far available.

New facts concerning the manifestation of tabby in Ta+/♀ either lend no support to the 'inactive X-chromosome' hypothesis or are at variance with it.

The tabby syndrome is also found in the autosomal genes for crinkled and (presumably) downless.

INTRODUCTION

The true extent of a syndrome is rarely suspected when a gene is first described. The sex-linked gene for tabby (Ta) in the mouse, and its autosomal mimics crinkled (cr) and downless (dl) were discovered as 'coat structure genes' (Falconer, Fraser & King, 1951; Falconer, 1953; Grünberg, 1966b, 1969; Claxton, 1967). Later, it was found that the syndrome includes characteristic anomalies of the teeth (Grünberg, 1965, 1966a; Sofaer, 1969). In this paper it will be shown that the syndrome is in fact much more pervasive and that it includes anomalies of a multitude of glands as well as a few surface features which had not been noticed previously. Many of the glands are absent altogether, others are more or less reduced, while some do not seem to be involved at all. The traditional methods of histology and embryology reveal a coherent situation which can be summarized in a single sentence. But when the distribution of

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the abnormalities is scrutinized in more detail, it is by no means obvious why some structures are affected whereas others are not. This, of course, reflects our general ignorance as to the mechanisms which, in normal development, lead to the complexity of structure and function in the derivatives of seemingly uniform surface epithelia. It may be hoped that a comparison of the tabby syndrome with others involving the same organs will ultimately help in understanding the underlying causalities.

The gene for tabby has in recent years figured often in the 'inactive X-chromosome' controversy. The present study is mainly concerned with the tabby male; but a few new facts concerning its manifestation in the heterozygous female will also be presented.

MATERIAL AND METHODS

Tabby embryos can easily be distinguished from their normal litter-mates by the absence of hair follicles from the 14-day stage onwards. The non-inbred stock segregating for $Ta$ was the same as that used for previous studies. In addition, genetically normal embryos ($F_2$ animals from a cross between the inbred strains CBA/Gr and C57BL/Gr) were used for earlier embryonic stages (11–13 days). Standard histological methods (Bouin fixation; H and E staining; sections of $10 \mu$) were used for the embryos; some newborn animals and later stages were fixed in formalin or Susa and sectioned at $15 \mu$.

Complete absence of a gland is easily diagnosed, but has to be distinguished from a mere delay in formation (such as happens with the coat). A marked reduction of a gland can generally be established by counting the number of sections in which it occurs. But complete normality is difficult to prove, and in some cases such a statement means no more than that there is no prima facie case to the contrary.

With the exception of the serous glands of the nose, little seems to be known about the anatomy and development of the minor glands in the mouse. Rather than spending an undue amount of time on a search through the literature, I have preferred to establish the facts necessary for the present investigation for myself; but, though a long list of glands has been examined, it is not exhaustive, and in a few instances the time of origin of a gland has not been determined. Where no rudiment is detectable on day $t$ but one is identifiable on day $t + 1$, it is held that the rudiment originated on day $t + 1$ if it is small; otherwise, interpolation is resorted to. This, however, is rather a rough and ready procedure for the following reasons. Some glands (e.g. Steno's gland in the nose) grow a surprisingly long duct within a day of the start; others (e.g. the Meibomian glands of the eyelids) make very little progress between their first appearance on day 17 and birth (which may be designated as day 20 post conceptionem). Yet others (like v. Ebner's glands of the tongue) arise on day 15, but make practically no progress beyond the bud stage for at least 2 days, a long time in the short gestation period of the mouse. Furthermore, in a few cases the
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The identity of the very first signs of a gland is not beyond dispute. Finally, there are limitations of the material. This consisted of serial sections (head and selected body regions) of one litter-mate pair each of 14-, 15- and 17-day embryos, of newborn and of 3-day animals, together with selected regions of pairs of animals of 5, 6, 10 and 21 days post partum (p.p.). Normal embryos (from CBA x C57BL F2) aged 11, 12 and 13 days were also examined, and for the 14-day (embryonic) stage there is the additional material used for the study of the tabby heterozygote (see below). For all these reasons, the time of origin is approximate only; it is believed, however, that the estimates are sufficiently accurate for the purposes of this paper.

Where possible, human anatomical terminology has been used. For the serous glands of the nose the terminology adopted is that of Broman (1921), who described these structures in detail. For the rest, in the absence of established names, I am using a topographical terminology of my own at the risk that some of these names may have to be changed as earlier ones come to light.

The nature of the secretions produced by the various glands is not always accurately known, or it is controversial (e.g. whether the glands in the pads of the murine foot are sweat or scent glands). As, for the purposes of this paper, glandular physiology is only of secondary importance, glands are referred to as ‘mucous’, ‘muco-serous’, etc., on the strength of H and E preparations alone.

The behaviour of the individual glands (and of a few other structures affected by the tabby gene) will be described on a regional basis. Embryonic ages referred to correspond to the developmental stages described previously (Grüneberg, 1943) rather than to the exact time an embryo has taken to reach a given stage. Presence or absence of a gland is symmetrical unless asymmetry is explicitly mentioned.

RESULTS

I. The tabby hemizygote

(1) The Harderian gland. This gland is situated behind the eyeball and opens on the nictitating membrane. Its rudiment is first detectable in the 14-day embryo; on the preceding day membrane and gland are not yet present. The epithelial moiety of the right gland was absent in a 17-day tabby foetus and in 3- and 5-day-old tabby young; both glands were present in a tabby newborn mouse. It is noteworthy that whenever the epithelial elements of the gland were missing, a well-defined ‘ghost gland’ of loose connective tissue, clearly identifiable by the characteristic melanocytes and its topography, was present. This ghost gland is a normal feature; in the normal 17-day foetus only its anterior region has become invaded by epithelial strands, the posterior region still being empty; at birth the glands are filled fairly completely, but those of the tabby were still half-empty like those of the normal 17-day foetus. Ultimately, glands of tabbies which have epithelial elements at all are about normally filled. Retardation of glandular rudiments was already detectable in 14- and 15-day
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tabby embryos, and at least one would probably not have resulted in a gland. Some Harderian glands of tabbies are thus absent altogether and others develop more slowly than normal.

(2) **The exorbital lacrimal gland.** The duct of this gland opens laterally into the conjunctiva of the lower eyelid; the gland itself is situated subcutaneously in front of and below the ear. The duct arises in the 14-day embryo and starts branching to form the gland in 15-day embryos. On casual inspection, this gland might appear normal in tabbies. However, in the 14-day embryo the duct is shorter; in a 15-day embryo the left duct is of normal length, but the gland itself is somewhat reduced; by contrast, the right duct is much shorter, ends diffusely and presumably no gland would have been formed. Later (17-day foetus, newborn), the ducts are longer but the glands rather smaller than normal. Hence, though the differences are not striking, they are probably real.

(3) **The intraorbital lacrimal gland.** This gland buds off the same duct which gives rise to the exorbital lacrimal gland, but only round about the time of birth; the gland occupies a position ventral to the eyeball. It is absent in 3- and 5-day tabbies, but represented by a ghost gland without glandular tissue proper as in the Harderian glands (though, of course, without melanocytes). In the newborn tabby mouse there is no outgrowth from the common duct, but the ghost glands can already be made out.

(4) **Glandulae tarsales (Meibomian glands).** The absence of these glands in crinkled (cr/cr) mice has already been described by Falconer *et al.* (1951). The same applies to tabby. In the normal, the glandular orifices can be seen, on eversion, as a row of fine unpigmented pin-pricks surrounded by pigmented skin on the edges of the eyelids. In the newborn normal mouse, short club-shaped ingrowths of epithelium are present, generally in corresponding positions on the upper and lower eyelids (which, at that stage, are fused with each other). In the 17-day foetus, what appear to be the very first indications of glandular development (cylindrical cells and a slight convexity towards the underlying mesoderm) can just be made out. The 17-day tabby has similar but smaller pre-glandular rudiments; these apparently fail to differentiate and regress, as no sign of them has been discovered in the newborn tabby mouse.

**The ear region**

(5) **Glandula ceruminosa.** The mouse has a single large ear-wax gland, the wide duct of which opens into the external auditory meatus not very far from the ear drum. The rudiment of the gland is first seen in the 15-day embryo and perhaps already arises at the 14½-day stage; it is not yet present at the 14-day stage, when tympanic cavity and external auditory meatus are still far apart from each other. In the tabby embryo the duct is shorter and subsequently the gland much smaller than in the normal mouse (followed to the 10-day stage *p.p.*). Though the glandular tissue is probably not more than about 5% in mass of that in the normal, the duct is far less reduced and of nearly normal calibre.
Sebaceous glands in external auditory meatus. In the normal mouse, fine hairs with large sebaceous glands occur deep in the meatus facing the tympanum. They are not yet present at birth, appear in the 3-day mouse and are fully differentiated in the 10-day animal. In the 3-day tabby mouse they are completely missing; in the 10-day tabby a few hairs have appeared, but these have only small sebaceous glands and not the large ones characteristic of the normal animal.

Fig. 1. (A) Longitudinal section through the anterior part of the head showing the orifices of the glandulae nasales mediales on the left side of the nasal septum; the glands themselves occupy the mucosa of the non-olfactory region of the septum. The position of Jacobson's organ is indicated by broken outline. (B) Longitudinal section, with the septum removed, showing the orifices of the gl. nasales laterales I–VIII (except that of IV which opens into the middle nasal duct and is not visible from this aspect).
The respiratory tract

The mouse has a large number of serous nasal glands most of which arise (open) in the vestibulum not very far from the orifice of the naso-lacrimal duct (Broman, 1921; Bojesen-Møller, 1964). Those formed early in development are remarkably constant and symmetrical and can be put into three major groups (Fig. 1). The *glandulae nasales mediales* occupy the non-olfactory mucosa of the nasal septum. The *glandulae nasales laterales* arise on the lateral wall of the nasal cavity on the maxillo-turbinal, the naso-turbinal and the intervening nasal duct.

![Diagram of nasal glands](image)

Fig. 2. Transverse sections through the nasal vestibulum of 14-day-old embryos (♂♀). In the tabby, gl. nasalis lateralis I (Steno’s gland) is normal; gl. nas. lat. III is reduced; gl. nas. medialis I is possibly represented by a slight swelling of material, which will not form a gland, and the remaining two glands are absent without trace.

The *glandulae nasales infraseptales* open near the orifice of the naso-lacrimal duct and the glands themselves occupy a position underneath the nasal septum. The positions of the orifices of the earlier of these glands are shown in Fig. 1. In addition, there are glands which open into the maxillary sinus, septal glands which open into Jacobson’s organ (organon vomeronasale) and, in the olfactory region of the nose, there are Bowman’s glands.

(7) *Glandulae nasales laterales*. Following Broman (1921), these are numbered in the order in which they arise. Gl. nas. lat. I (also known as Steno’s gland, after the Danish anatomist who described it as early as 1664 in the sheep) differs from the other glands of this group in that its duct has a lumen from the very beginning (see Fig. 2), i.e. day 12 of embryonic life; the long duct leads back to the maxillary sinus, where the gland thickly covers most of the lower part of the cavity. Gl. nas. lat. II and III (Fig. 2) arise on day 14 and IV on day 15 (actually, its beginnings are already present in some ‘premature’ 14-day embryos). The other glands up to VIII are formed on days 15 and 16; later glands become
increasingly less constant and have not been studied in detail. In the tabbies, Steno’s gland appears to be completely normal. Gl. nas. lat. III is rudimentary from the start (Fig. 2) and forms a correspondingly reduced gland (followed up to 3 days p.p.). Gl. nas. lat. IV is present and apparently normal. All other lateral glands (i.e. II, V–VIII and beyond) are completely absent.

(8) *Glandulae nasales mediales*. Glands I and II form in the 14-day embryo (Fig. 2), III and IV a day later. All of them are absent in tabbies.

(9) *Glandulae nasales infraseptales*. There are two of these, the smaller anterior and the larger posterior, which open in close proximity to the orifice of the naso-lacrimal duct. In disagreement with Broman (1921), I find that the posterior gland arises on day 14 and the anterior one on day 15. Both of them are completely missing in tabbies.

(10) *Glandulae propriae sinus maxillaris*. These glands arise (open) with many short ducts from that region of the maxillary sinus which is not occupied by Steno’s gland; the glands which arise on day 15 are completely normal in tabbies.

(11) *Glandula anterior organi Jacobsoni*. This gland which opens anteriorly into Jacobson’s organ arises on day 15. Like others formed later from this organ, it is normal in tabby.

(12) *Bowman’s glands*. These small glands which are peculiar to the olfactory region can first be identified in the 17-day foetus. They are normal in tabby.

(13) *Glandulae mucosae tubae auditivae* (Fig. 3). These glands arise with many ducts from the Eustachian tube and neighbouring regions of the nasopharynx. The ducts penetrate the muscle coat of the pharynx and the gland proper comes to lie under the base of the skull in the angle formed by the os sphenoidale aborale and the auditory capsule. The gland arises late in development, being still absent in the 17-day foetus and insignificant in the newborn mouse; the time of onset may be estimated at 18–19 days. The gland is missing in tabby.

(14) *Glandulae nasopharyngeae*. These small (? serous) glands arise in large numbers from the sides of the nasopharynx behind (13); the glands remain within the muscle coat of the pharynx and have first been seen in the normal 17-day foetus. None are present in tabby.

(15) *Glandulae epiglotticae, laryngeales and tracheales*. In the normal mouse, (? mucous) glands are present on the paries laryngea epiglottidis, on the larynx next to the epiglottis, in the neighbourhood of the plicae aryepiglotticae and (mainly dorsally) down to the region of the first 1–3 rings of the trachea. These glands are present at birth; they are absent in tabby (followed to 10 days p.p.). The time of origin of these glands has not been determined.

The digestive tract

(16) *The teeth*. The dental part of the tabby syndrome has been described in detail by Grünneberg (1965, 1966a) and by Sofaer (1969). A thickened dental lamina is present in the normal 12-day embryo, and downgrowth of epithelium
is advanced in the 13-day stage. As with some of the glands, the question arises as to whether the onset of dental development should be counted from the thickening of the epithelium or from its downgrowth into the membrana propria.

(17) The papilla vallata of the tongue. The mouse has a single papilla vallata; some of the glands of v. Ebner (no. 22 below) open into the moat surrounding it (Fig. 3). A typical papilla vallata (at that time closely associated with a nerve trunk derived from the nervus glossopharyngeus) appears in the normal 14-day embryo. In the 13-day embryo it is preceded by a median (longitudinal) groove the possible relation of which to the foramen caecum has not been studied. It looks as if the circular downgrowth of epithelium around the nerve trunk leads to the disappearance of the groove. In tabby (Fig. 4) the downgrowth of epithelium remains rudimentary and the groove persists as a longitudinal slit which can easily be seen from the surface throughout life.

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Fig. 3. Semidiagrammatic section through the region of the Eustachian tubes, the tympanic cavity and the radix linguae to show the position of some of the glands mentioned in the text. The drawing is a reconstruction which represents a slice of tissue about 1.4 mm thick which thus includes structures which are not in the same plane. (1) Gl. mucosae tubae auditivae. (2) Gl. palatinae. (3) Gl. glossopalatina. (4) Papilla vallata. (5, 6) Two types of glands treated together in the text under the name of gl. linguales laterales. (7) Gl. linguales mediales (v. Ebner) opening on the surface of the radix linguae. (8) The same kind of gland, opening into the moat of the papilla vallata. In the lateral wall of the collapsed external acoustic meatus, the large sebaceous glands associated with fine hairlets are visible. Based on preparations from a 3-day-old normal mouse ♂.
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(18) Glandula sebacea anguli oris. Just inside the mouth there is a large sebaceous gland which arises from a number of separate buds in the 15-day stage; none are present in the corresponding tabby embryo. The gland opens into an elongated deep pit behind the corner of the mouth, with the glandular tissue exclusively ventral to the pit (i.e. in the continuation of the lower lip). The gland makes a belated appearance in tabbies but remains smaller than normal (followed up to 3 days p.p.).

Fig. 4. Transverse sections through the papilla vallata of a normal (A) and a tabby (B) 15-day embryo (litter-mates). The rudimentary downgrowth of epithelium in the tabby embryo indicated by arrows.

(19) The large salivary glands. In the normal the parotid and submaxillary glands originate in the 12-day, the major sublingual gland in the 13-day and the accessory parotid in the 15-day embryo. All of them appear to be normal or nearly so in tabby. The ducts of the submaxillary and the major sublingual glands have a lumen from the beginning.

(20) Glandula buccalis. In the normal mouse a small and fairly compact (? mucous) gland buds off in the neighbourhood of the second lower molar. It arises in the 15-day embryo. The gland is missing in tabbies (followed to 3 days p.p.).

(21) Glandulae linguales laterales. The anterior part of the mouse tongue lacks glands. A little in front of the level of the papilla vallata, and opening laterally on the dorsum linguæ (see Fig. 3), there are some compact (? mucous) glands in the substance of the tongue. In the normal, they arise in the 15-day embryo. They are absent in tabby (followed to 10 days p.p.).

(22) Glandulae linguales mediales (v. Ebner). Many of these (? serous) glands
open on the radix linguae (see Fig. 3), where their orifices can easily be seen from
the surface, others open into the moat of the papilla vallata. In the normal they
arise in the 15-day stage. In tabby they are absent at first; at birth, questionable
rudiments can be seen at the bottom of the 'moat'; by the 5-day stage very
rudimentary glands are present, and by 10 days some further progress has been
made though the glands are still scanty as compared with the normal. These
glands thus arise after a delay, and apparently do not reach normality.

(23) **Glandulae palatinae.** Numerous (?) mucous glands which open with short
ducts along the length of the palate. Those on the soft palate arise at the 17-day
stage, the remainder before birth. The glands are completely absent in tabby
(followed to 5 days p.p.). At that stage it can be seen in the normal mouse that,
in addition to the mucous glands which open ventrally on the soft palate, there
are other (?) serous glands which open dorsally into the nasopharynx; they also
are absent in tabby.

(24) **Glandula glosso-palatina.** With this name we may designate a (?) mucous
gland whose duct opens laterally far back on the soft palate, but whose
glandular tissue is embedded in the lateral part of the radix linguae (Fig. 3).
The gland arises in the 15-day embryo. It is absent in tabby (followed to 10
days p.p.).

(25) **Glandulae pharyngeae.** One can distinguish between glandulae pharyn-
geae laterales, a compact group of glands which originate on the lateral margin
of the pharynx a little before the end of the soft palate and come to lie close to
the otic capsule, and the glandulae pharyngeae posteriores: the latter are
numerous glands which originate independently of each other from the lateral
and posterior wall of the nasopharynx and as far down as the beginning of the
oesophagus where they come to an end. Both groups of glands are completely
absent in the newborn tabby. The time of onset of these glands has not been
determined.

(26) No abnormalities have been discovered in the glands of the stomach,
the duodenum (including Brunner’s glands), the small intestine, the colon and
the rectum. Similarly, the pancreas (including the islets of Langerhans) and the
liver appear to be normal.

(27) **The anal glands.** In the normal mouse a large group of (sebaceous) anal
glands surrounds, like a plate, the whole anus and anteriorly comes to lie between
layers of the sphincter muscles. Buds of these glands are first detectable in the
newborn mouse; to judge from their size, the onset is in the 19-day foetus. The
anal glands are completely missing in tabby (followed to 21 days p.p.).

**The urogenital tract**

The glands of the urogenital tract have not been examined as completely as
those of the rest of the body, and there are several obvious omissions.

(28) **Glandula praeputialis.** This large, flat and approximately triangular
(?) sebaceous) gland opens with a single strong duct near the free margin of the
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praeputium. The gland originates in the 13-day embryo (as does the corresponding glandula clitoridis in the ♀). It is absent without any trace in tabby (followed to 21 days p.p.).

(29) Other sebaceous glands in the urogenital region. The ano-genital region has very fine hairs which have, however, large sebaceous glands. In particular, the praeputial hairs are often completely surrounded by such glands. In the tabby ♂ (21 days p.p.) the hairs are few in number and the sebaceous glands small in size.

(30) Glandulae urethrales (Littré). These glands surround the proximal (membranous) region of the urethra. Those of tabby do not seem to differ appreciably from the normal.

(31) Glandulae bulbo-urethrales (Cowper). In the 21-day tabby male this gland appears to be smaller than that of the normal brother; but as the maturation of the genital organs is generally retarded, not much importance can be attached to this finding.

(32) As seen in dissections of adult males, the vesicular glands ('seminal vesicles') and the coagulating glands appear to be about normal. These glands were not examined histologically.

Palma and planta

(33) Sweat (? scent) glands (Fig. 5). The mouse has no sweat glands in its hairy skin. It has, however, characteristic glands in the terminal pads of the digits and the pads of palma and planta (Schaffer, 1940). In the forelimbs these first appear in the 17-day foetus; those of the hind limbs soon after, if slightly uncertain indications have been correctly interpreted. The glands are absent in tabby (followed to 21 days p.p.).

(34) Plicae digitales (Fig. 5). On their ventral surface the digits of the mouse and other rodents have deeply indented transverse folds, about 7–8 in number on the longer digits of the hind limbs and less in front; some of the sweat glands open at the bottom of these indentations. Plicae digitales are not yet present in the 17-day foetus, and those in the newborn mouse are still immature; their estimated onset is at about day 18 of foetal life. Plicae digitales are permanently absent in tabby as are the digital scales which resemble those in the tail rings.

II. The tabby heterozygote

(35) The early development of the coat. In the course of this work it was noticed that 14-day embryos segregating for tabby seemed to include (in addition to naked Ta embryos) some with fully developed ('normal') and others with uniformly retarded ('intermediate') hair follicles. Thus, there were 77 'normals', 23 'intermediates' and 31 naked tabbies in fifteen litters of embryos from Ta/+ ♀ × ♂ matings. The suspicion arose that the 'intermediates' might be the Ta/+ ♀♀, but as 77:23 is a poor fit to a 2:1 ratio (x² = 4.805), a few Ta/+ ♀♀ may be included in the 'normal' class. For a more critical test, 14-day embryos
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from $+/+ \times Ta^T$ matings were examined in which all the $\delta\delta$ should be 'normals' and most or all the $\varphi\varphi$ should be $Ta/+$, 'intermediates'. The embryos were classified by inspection and subsequently sexed histologically; the nasal region was also sectioned. The material included four litters with 16 'intermediates' all of which turned out to be $\varphi\varphi$, and 12 'normals' of which 11 were $\delta\delta$ and one a $\varphi$. This close agreement with expectation is extremely unlikely to be due to chance alone. On the other hand, there remained the possibility that at the 14-day stage, coat development of $\delta\delta$ is somewhat ahead of that of $\varphi\varphi$. As a test, two litters of 14-day embryos not carrying the tabby gene (from CBA x C57BL crosses) were examined; these contained six 'normals' and six 'intermediates'; but this time the 'normals' included three $\delta\delta$ and three $\varphi\varphi$ and the 'intermediates' one $\delta$ and five $\varphi$. Evidently, in this case, classification has been by degree of maturity and irrespective of sex. This was independently confirmed from the development of the nasal glands. All six 'normals' had the full complement of gl. nas. lat. I—III and gl. nas. med. I—II and four of them showed the beginnings of gl. nas. lat. IV; by contrast, four of the 'intermediates' still lacked the gl. nas. lat. III and med. II. It must be concluded that 'intermediacy' in the segregating litters is due to the presence of $Ta$ in heterozygous condition rather than to sex as such. However, there are still two possibilities. Tabby may affect the hair follicles specifically or only indirectly through a general retardation of development. The latter possibility is not supported by the examination of the nasal glands. The usual complement at the 14-day stage is gl. nas. lat. I—III and med. I+II, and this is present in the 11 normal $\delta\delta$, the 'normal' ($Ta/+\delta$) $\varphi$ and in 13 'intermediate' $Ta/+\varphi\varphi$; four of the $\delta\delta$ and one of the $\varphi\varphi$ also had the beginnings of gl. nas. lat. IV symmetrically; one $\varphi$ lacked both medial glands but had the three lateral ones which is difficult to explain by immaturity; only two of the $\varphi\varphi$ can be so accounted for. Evidently, tabby acts on the coat specifically and is thus semi-dominant in this respect. The coat is affected uniformly and shows no sign of naked tabby stripes; the striped pattern subsequently found in the coat is probably superimposed on it by the transverse wrinkling of the skin in the 15- to 16-day stage (Grüneberg, 1966b).

**Figure 5**

(A) Longitudinal section through a digit of the right hind foot; normal 17-day foetus. At this stage there is no sign of the plicae digitales, and though there are sweat-gland rudiments in the forelimbs, none can be identified with certainty in the hind limbs. Bouin fixation; H and E; 10 $\mu$. x65.

(B) Longitudinal section as above; normal newborn mouse. Plicae digitales have now made their appearance, but they have not yet reached their full depth or separated from each other. Note the presence of sweat glands in the distal pad. Bouin fixation; H and E; 15 $\mu$. x51.

(C) Longitudinal section as above; normal mouse, 3 days old. Plicae digitales are now in their final state; note that a sweat gland opens into the third of these folds as counted from the tip. The sweat glands have grown in size. Technique as under (B).
Plicae digitales. Their absence in tabby $\delta\delta$ (no. 34) finds no counterpart in $Ta/ + \varnothing\varnothing$. The four feet of 14 $Ta/ + \varnothing\varnothing$ ($= 252$ digits) were fixed in formalin and scrutinized under the dissecting microscope. Normal plicae digitales were present throughout; hence there is no sign of patchy manifestation such as would be expected under the 'inactive X-chromosome' hypothesis.

Glandulae tarsales (Meibomian glands). About 11-12 glands are normally present per eyelid. The four lids of 13 genetically normal mice of both sexes from segregating matings averaged 46-1 glands. Seven $Ta/ + \varnothing\varnothing$ averaged 37-3 glands; 10 out of their 28 eyelids had complete sets of glands (average 11-5 glands) and 18 were reduced (average 8-1 glands). Altogether, about 19% of the glands were thus missing in $Ta/ + \varnothing\varnothing$. Presence or absence is evidently a threshold phenomenon like that of the Harderian glands in tabby $\delta\delta$. Tabby is thus semi-dominant as regards these glands, but the heterozygote is nearer the normal than the mutant phenotype.

Glandulae nasales. As already mentioned (no. 35), normal complements of these glands were found in 14 out of 17 $Taj + \varnothing\varnothing$ (14-day embryos). Two of the remaining $\varnothing\varnothing$ lacked symmetrically gl. nas. med. II which is presumably a sign of immaturity. Only one $\varnothing$ with symmetrical absence of both medial glands in the presence of the three lateral ones might conceivably be due to semi-dominance of $Ta$; if so, it reveals no sign of patchy manifestation.

**DISCUSSION**

The tabby syndrome consists of anomalies of the sinus hairs, the coat, the teeth, many glands and some surface structures such as the papilla vallata, the tail rings and the plicae digitales. All these have one feature in common: *they all arise by the downgrowth of a surface epithelium into the membrana propria*. This is equally true for hair follicles, the dental lamina, the ducts of glands and the infolding of the plicae digitales and similar structures. On the other hand, not all structures which arise in this way are affected by the tabby gene. The question must therefore be asked as to why certain organs escape whereas others are mildly or severely affected.

One time-honoured (though generally empty) concept can easily be disposed of. The majority of the abnormal structures are of ectodermal origin, but this does not apply to gl. epiglotticae, laryngeae and tracheales which are derived from the endoderm, and the same is probably true for the glands which arise from the dorsal surface of the pharynx.

The great diversity of the structures affected also immediately rules out the possibility that the common denominator is similarity of function, and hence histogenetic (i.e. histochemical) similarity.

A time concept of gene action for the coat manifestations of crinkled (and, by implication, of tabby) has been suggested by Falconer et al. (1951). 'The formation of new hair follicles is suppressed between 12½ and 17 days of gesta-
Glandular aspects of tabby syndrome

tion, and again from the time of birth onwards.’ If those hair types which are
absent from the coats of the mutants are normally produced during the periods
of follicle suppression, the syndrome as known at that time is reduced to a uni-
tary formulation. Can a time concept account for the pattern of the syndrome
as we know it now? To test this possibility, all those effects of tabby are shown
in Table 1 for which the time of onset in embryonic development is known with

Table 1. Involvement of glands and other structures and their time of onset

<table>
<thead>
<tr>
<th>Onset (days of gestation)</th>
<th>Structure</th>
<th>Normal</th>
<th>Reduced</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>Parotid</td>
<td></td>
<td>+</td>
<td>.</td>
</tr>
<tr>
<td></td>
<td>Submaxillary gland</td>
<td>+</td>
<td>.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gl. nas. lat. I (Steno’s gland)</td>
<td>+</td>
<td>.</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Secondary vibrissae</td>
<td>+</td>
<td>+</td>
<td>.</td>
</tr>
<tr>
<td></td>
<td>Molars</td>
<td>.</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Major sublingual gland</td>
<td>+</td>
<td>.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gl. praeputialis</td>
<td>.</td>
<td>.</td>
<td>+</td>
</tr>
<tr>
<td>14</td>
<td>Hair follicles</td>
<td>.</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Harderian gland</td>
<td>.</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exorbital lacrimal gland</td>
<td>.</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gl. nas. lat. II</td>
<td>.</td>
<td>.</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Gl. nas. lat. III</td>
<td>.</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gl. nas. med. I and II</td>
<td>.</td>
<td>.</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Gl. nas. infraseptalis posterior</td>
<td>.</td>
<td>.</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Papilla vallata of tongue</td>
<td>.</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Gl. ceruminosa</td>
<td>.</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gl. nas. lat. IV</td>
<td>+</td>
<td>.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gl. nas. lat. V-VIII</td>
<td>.</td>
<td>.</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Gl. nas. med. III and IV</td>
<td>.</td>
<td>.</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Gl. nas. infraseptalis anterior</td>
<td>.</td>
<td>.</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Gl. propriae sinus maxillaris</td>
<td>+</td>
<td>.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gl. anterior organi Jacobsoni</td>
<td>+</td>
<td>.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Accessory parotid</td>
<td>+</td>
<td>.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gl. sebacea anguli oris</td>
<td>.</td>
<td>+</td>
<td></td>
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<tr>
<td></td>
<td>Gl. buccalis</td>
<td>.</td>
<td>.</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Gl. lingualis lateralis</td>
<td>.</td>
<td>.</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Gl. linguales mediales (v. Ebner)</td>
<td>.</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gl. glossopalatina</td>
<td>.</td>
<td>.</td>
<td>+</td>
</tr>
<tr>
<td>17</td>
<td>Gl. tarsales (Meibomian glands)</td>
<td>.</td>
<td>.</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Bowman’s glands</td>
<td>+</td>
<td>.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gl. nasopharyngeae</td>
<td>.</td>
<td>.</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Gl. palatinae</td>
<td>.</td>
<td>.</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Sweat (? scent) glands, fore feet</td>
<td>.</td>
<td>.</td>
<td>+</td>
</tr>
<tr>
<td>18?</td>
<td>Plicae digitales</td>
<td>.</td>
<td>.</td>
<td>+</td>
</tr>
<tr>
<td>19</td>
<td>Intraorbital lacrimal gland</td>
<td>.</td>
<td>.</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Gl. mucosae tubae auditivae</td>
<td>.</td>
<td>.</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Anal glands</td>
<td>.</td>
<td>.</td>
<td>+</td>
</tr>
<tr>
<td>3 days p-p.</td>
<td>Sebaceous glands, ext. auditory meatus</td>
<td>.</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>
reasonable accuracy. A given structure is classified as ‘normal’ (or nearly so); as regularly and symmetrically ‘absent’; or as ‘reduced’ if it is sometimes absent (like the Harderian glands), or reduced in size (like the gl. ceruminosa), or forms after a delay (like the coat or the gl. linguales mediales), or if it is otherwise structurally abnormal (like the molars or the papilla vallata).

There are no known effects of the tabby gene prior to the 13-day stage. From that day onwards until the time of birth, organs, as they are formed, may be normal, reduced or absent in tabby. Perhaps there is a general tendency for organs which are formed late to be more often involved than organs which form early. However, it is not possible to specify a time such that organs formed before it are all normal and organs formed after it are all affected. Table 1 suggests that once it has arisen, the tabby ‘state’ continues throughout life. This also agrees with the continued production of structurally abnormal hairs; since a given hair follicle does not seem to be irreversibly determined as to the kind of hair it forms (see Grünberg, 1969, for the relation of flails and awls in tabby), it seems reasonable to assume that hair growth and differentiation is under the active control of the gene in the adult.

In view of the heterogeneity of the entities in Table 1, it is perhaps instructive to test the time concept also separately in a homogeneous category like the gl. nasales laterales which arise in close proximity to each other, but in a definite time sequence. They are, in order of their formation

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>normal</td>
</tr>
<tr>
<td>II</td>
<td>absent</td>
</tr>
<tr>
<td>III</td>
<td>reduced</td>
</tr>
<tr>
<td>IV</td>
<td>normal</td>
</tr>
<tr>
<td>V-VIII</td>
<td>absent</td>
</tr>
</tbody>
</table>

This kind of situation cannot plausibly be explained by a time concept of gene action, and this conclusion appears inescapable whichever way the data of Table 1 are viewed.

We thus come to the conclusion that the pattern of the tabby syndrome cannot be explained by common origin from a single germ layer, nor by common function of the structures affected, nor by a time concept of gene action.

Of all the effects of tabby so far discovered, only two minor ones are clearly secondary. As already pointed out by Falconer et al. (1951), the small terminal tail kinks commonly found are due to the fact that the tail skin is a trifle too small in relation to the skeleton. It is also now clear that the accumulation of hairs, etc., in the nose which leads to the ‘snuffling’ of tabbies is almost certainly a consequence of their defective nasal glands. The other anomalies appear to be coordinated in the sense that they have a common root cause and that none is the cause of another. They are, however, not necessarily all independent of each other: the exorbital lacrimal gland (which originates on day 14) is ‘reduced’ in tabby, and the intraorbital lacrimal gland (which in normal development buds
from the same duct on day 19) is absent. More relations between glands may come to light in studies of other genes with glandular involvements which are now in progress.

With the exception of these two secondary effects, all the anomalies of tabbies involve structures derived from a surface epithelium. It may therefore be suspected that this is the seat of primary gene action. If so, why do some derivatives of surface epithelia escape unscathed? Conversely, the fault may lie with the mechanism(s) in the underlying membrana propria which elicits the downgrowth of epithelium in some places, but not in others. As is well known, the full potentialities of surface epithelia are not realized in normal development; for instance, in extra-toes (Xt/XT; Johnson, 1967) in the mouse an anomalous configuration of the forehead is accompanied by the formation of sinus hairs in places where none are present in the normal animal. A stimulus is thus always required to elicit local growth of the surface epithelium, and it might be suggested that the primary disturbance is in the membrana propria, not in the surface layer. Again, why in some places and not in others? Thirdly, it might be suggested that the fault does not lie with one or with the other, but with the interaction between the two. The situation might be analogous to that in anophthalmia in the mouse (Chase & Chase, 1941) where usually the eye-cup does not get close enough to the overlying epidermis to induce a lens, and in the absence of a lens, the eye-cup regresses: but, in the rare instances where the eye-cup gets close enough, it can be seen that it is capable of inducing a lens and also that the epidermis is competent to react to the eye-cup—the essence of the anomaly is thus a lack of interaction.

It seems least likely that the fault lies with the membrana propria. In several instances in the 'reduced' category in Table 1, the signal for downgrowth has obviously been given, but it is not always answered or the structure formed is rudimentary. Particularly striking are the cases of the Harderian gland and of the intraorbital lacrimal gland, where a mesodermal ghost is present in the absence of the ectodermal moiety of the gland.

It is not too difficult to visualize a situation in which the surface epithelium is the culprit. Supposing its response to normal stimuli from the mesoderm were lowered, it might still respond normally in some places but not in others.

An anomaly of interaction between epithelium and membrana propria might be visible at their interface. Suspicious configurations have indeed been noticed on several occasions, but a more detailed investigation will be required to assess their significance. Perhaps ultrastructural studies by means of the electron microscope will help. Regional differences in interaction could, of course, give rise to regional differences in gene manifestation. For instance, if a sub-epidermal oedema were at the bottom of the syndrome, differences in its intensity in time and space could be responsible for the pattern.

As a 3-day-old crinkled $g$ had no plicae digitales, but a slit-like papilla vallata like tabby, and as it lacked both the preputial and the anal glands, not to mention
the Meibomian glands already described by Falconer et al. (1951), there is little doubt that crinkled has the full tabby syndrome. The same presumably applies to downless which was not available for examination.

Finally, the manifestation of several new features in $Ta/+ \, \varnothing \varnothing$ gives no support to the ‘inactive $X$-chromosome’ hypothesis. The uniformly retarded (intermediate) development of the coat in 14-day embryos indicates the simultaneous action of both alleles over the whole body; and the recessive behaviour of the plicae digitales and of the serous glands of the nose could only be fitted into the hypothesis on the $ad\, hoc$ assumption that both features develop non-autonomously. All this is not surprising in view of the fact that it has been shown (Grüneberg, 1966a, b, 1969), that tabby does not behave according to that hypothesis.

**ZUSAMMENFASSUNG**

_Die Drüsen beim Tabby-Syndrom der Maus_


Neue Tatsachen betreffend die Manifestierung von tabby bei $Ta/+ \, \varnothing \varnothing$ geben entweder keine Stütze für die Lyon-Hypothese oder sind mit ihr unverträglich.

Das Tabby-Syndrom kommt auch bei den autosomal Genen für crinkled und (vermutlich) downless vor.

The author is much indebted to Mr A. J. Lee for the illustrations, and particularly to Miss Beryl F. Fannon who made all the preparations on which this paper is based.

**REFERENCES**


Glandular aspects of tabby syndrome


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