

LETTER TO JMG

From Aldrovandi's "Homuncio" (1592) to Buffon's girl (1749) and the "Wart Man" of Tilesius (1793): antique illustrations of mosaicism in neurofibromatosis?

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Neurofibromatosis type 1 (NF1) and type 2 both occur in mosaic (segmental) forms.¹ When NF1 (and other autosomal dominant skin disorders)^{1,2} occurs in a linear, patchy, quadrant, or otherwise localised form, two different types of mosaicism can be distinguished.² Type 1 segmental involvement reflects heterozygosity for a postzygotic mutation occurring in an otherwise healthy embryo. The segmental lesions are limited to the affected area and show the same degree of severity as that found in the corresponding non-mosaic trait (for example, mosaic/segmental NF1). Type 2 segmental involvement occurs in a heterozygous embryo and reflects loss of heterozygosity that occurred at an early developmental stage. Clinically, the lesions of type 2 segmental involvement are markedly more pronounced and superimposed on a milder, non-segmental, heterozygous manifestation of the same trait.² In the light of these concepts of mosaicism, we critically reviewed (previously published) antique illustrations of presumed "full blown" NF1 sufferers.³⁻⁹ We have diagnosed as having mosaic/segmental NF1 the Indian



Figure 1 The illustration of the "Homuncio" (p 597) accompanying Aldrovandi's case report in "Monstrorum Historia" (1642) © S Karger AG and University Library of Bologna.

Key points

- Neurofibromatosis type 1 (NF1) and type 2 both occur in mosaic (segmental) forms: the segmental lesions can be limited either to the affected area showing the same degree of severity as that found in the corresponding non-mosaic trait (type 1/segmental involvement) or are markedly more pronounced and superimposed on a milder, non-segmental, heterozygous manifestation of the same trait (type 2 segmental involvement).
- By critically reviewing antique illustrations of presumed "full blown" NF1 sufferers, we have diagnosed as having mosaic/segmental NF1 the Indian man ("Homuncio") in "Monstrorum Historia" by Ulisse Aldrovandi (1522-1605), the horned monster in "Des Monstres et Prodiges" by the French surgeon Ambroise Paré (1510-1590), and the goitred woman in "Buch der Natur" by the German naturalist Conrad von Megenberg (1303-1374). Type 2 segmental manifestations of NF1 were recognisable in Buffon's girl (1707-1788) and the "Wart Man" of Tilesius (1793).
- These antique illustrations may be considered as the earliest examples of mosaicism in neurofibromatosis.

man ("Homuncio") in the "Monstrorum Historia"¹⁰ of the Italian naturalist and philosopher Ulisse Aldrovandi (1522-1605), the horned monster in "Des Monstres et Prodiges"¹¹ of the French surgeon Ambroise Paré (1510-1590), and the goitred woman in the "Buch der Natur"¹² of the German naturalist Conrad von Megenberg (1303-1374). Type 2 segmental manifestations of NF1 were recognisable in Buffon's girl (1707-1788)¹³ and the "Wart Man" of Tilesius (1793).¹⁴

ALDROVANDI'S DOCUMENTS IN BOLOGNA

In 1592, Ulisse Aldrovandi (1522-1605), an Italian physician, philosopher, and naturalist,¹⁵ recorded the extraordinary case of a man of short stature ("Homuncio"), of Indian origin, who presented enormous, flabby masses of flesh less than two inches thick hanging from the left side of his head and trunk (fig 1).^{3,4,10} This illustration, along with a Latin text (fig 2), appeared on pages 587 and 585, respectively, of "Monstrorum Historia", published posthumously in 1642 under Aldrovandi's name and edited by Bartolomeo Ambrosino.¹⁰ Zanca and Zanca^{3,4} have stated that this case report is a modified version of one written by an amanuensis and found among Aldrovandi's documents in the University Library in Bologna in a tome containing stories and chronicles regarding the period between 12 November 1592 and June 1593 (f 145, ms 136, tome XIX).³ They also implied^{3,4} that this misshapen man would represent a multiple (type 1) neurofibromatosis-like case.^{5,7,9}

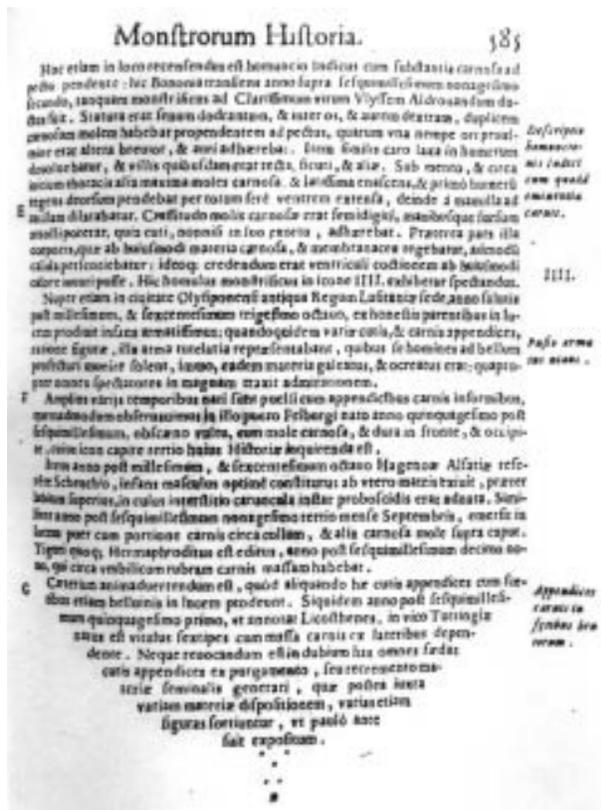


Figure 2 The 1642 Latin version in Aldrovandi's "*Monstrorum Historia*" (p 585) describing the "*Homuncio*". Its first lines read (paragraph E): "In this place also must be considered the Indian man of short stature with a fleshy substance hanging from [?] the chest. Passing through Bologna previously in the year 1592 this misshapen man was brought to the most distinguished gentleman Ulisse Aldrovandi". © S Karger AG and University Library of Bologna.

THE "HOMUNCIO"

The earlier version (1592) of Aldrovandi's manuscript has been transcribed and translated in Italian by Zanca³ with the help of R Signorini. The English translation of this original version reads: "The monster, Homunculus, as refers the Aegisthus, born in India, of six palms in stature. Between his mouth and left ear, he had a double fleshy mass hanging forward towards the chest: one [mass] was nearer the mouth, the other shorter, and adhered to the ear. Behind and under the left ear, likewise, a similar flesh rolled down dropping over the shoulder, spread with some tufts of hair as were the former two [masses] on the left side of his mouth covered with hairs such as of beard, particularly in the folds. At the beginning of the chest, under the chin and springing up around almost the entire chest, another very large and very wide [fleshy mass] extending from the left shoulder hung downward across almost the entire abdomen, enlarging from the right breast to the opposite side or rather the left armpit. Indeed that flesh and that loose substance was less than two fingers thick and with the hands it could be raised from the body, as it did not adhere [to the skin] except in the place of its own origin, up to the beginning of the chest and over the breasts. That same part of the body felt exceedingly warm, and therefore it must be believed that the red portion of the growth could be invaded by heat of some kind. This monstrous homunculus was brought to my attention by the Bolognese nobleman Bovio."

An English translation⁵ of the (later) version (fig 2) found in Aldrovandi's "*Monstrorum Historia*" (1642)¹⁰ contains a few modifications compared to the earlier version.³

Zanca³ purported that the person who carried out the xylograph forgot to copy the drawing in reverse onto the wooden

tablet, so that the illustration, once engraved, showed the fleshy masses to originate on the right side of the body (fig 1) rather than the left, as described in the original report found among Aldrovandi's documents.^{3, 5}

ULISSE ALDROVANDI AND HIS TIME: THE RENAISSANCE CONCEPTION OF MONSTERS

Certainly, Aldrovandi's Indian man should be viewed in the context of Renaissance European conceptions of monsters originating from the old Greek notion of ethnographical monsters, which they imagined to live far away in the east, above all in India.⁵ Indeed, Wittkower¹⁶ describes Aldrovandi as a scholar of immense erudition but at the same time somewhat more accepting and uncritical of tales and myths about human and animal monstrosities, calamities, and political or religious upheavals of the old authorities than one might expect.^{4, 5} In "*Monstrorum Historia*", the "fabulous races" appear one after the other in large woodcuts accompanied by learned texts. Nonetheless, one feels that we are dealing, in this instance (figs 1 and 2), with a really scientific illustration because of the accuracy of detail in the portrait and the accompanying text and its likeness to the phenotype of a neurofibromatosis sufferer.

It must also be also noted that Aldrovandi used to draw portraits and engrave thousands of illustrations of animals, plants, and minerals, of which quite a few are kept in the University Library of Bologna.^{3, 15, 17} Such illustrations are exceedingly accurate (Aldrovandi was among the first to give importance to colour figures) aiming to form the basis of an encyclopaedia of natural history in 13 volumes published, almost entirely posthumously, by Aldrovandi's pupils who took 73 years to complete it.^{3, 15} In addition, Aldrovandi reported and illustrated meticulously several dermatological conditions with monstrosities.^{15, 17}

DID THE "HOMUNCIO" HAVE FULL BLOWN NEUROFIBROMATOSIS TYPE 1?

Zanca and Zanca^{3, 4} based their diagnosis of NF1 on (1) the appearance of the masses (looking like plexiform neurofibromas)^{18, 19} covered with hairs (similar to the hairy naevi seen in NF1),²⁰ and (2) the short stature of the subject (a minor NF1 feature)^{20, 21} ascribed to a "grave form of widespread kyphoscoliosis (an NF1 complication)^{20, 22} or to a serious endocrinal alteration". They implied that "the phenomenon of striking tumours covered with hairs can be observed, with or without other congenital anomalies, in von Recklinghausen disease".⁴ Madigan and Masello,⁵ in confirming the diagnosis of NF1, added macrodactyly of the left second toe and leg asymmetry (fig 1) secondary to scoliosis as additional clinical stigmata of NF1.

REDIAGNOSING THE "HOMUNCIO": MOSAIC (SEGMENTAL) NF1

We think that the diagnosis of "full blown" (generalised) NF1 in this case³⁻⁹ should be reconsidered in light of the concept of mosaicism in the neurofibromatoses¹ and more generally in human skin disorders.^{2, 23}

This portrait (fig 1) is a xylograph copy reproducing the body of the "*Homuncio*" in its minute detail, the flaccidity of soft tissues, the skin folds, the lack of adherence of the mass to the skin, the hairs covering (only) part of the skin in the nearby area of the mass on the right arm and shoulder, the (apparent) multiplicity of the masses, are all for the meticulous reproduction of a patient rather than as an illustration of a mythological monster. The accompanying Latin description (fig 2) is even more detailed than the illustration itself. If the diagnosis were that of "full blown" NF1 then one would have expected a more "generalised" NF1 phenotype, especially if one considers the associated severe complications (for example, the plexiform neurofibroma and



Figure 3 The “horned” monster born on 17 January 1578 in Piedmont, in Chieri, near Turin, Italy as illustrated in Ambroise Paré’s “*Des Monstres et Prodiges*”, Paris 1585. © S Karger AG.

the scoliosis). Conversely, this detailed case lacks depiction of other (classical) clinical features of NF1 (for example, café au lait spots, freckling, or cutaneous neurofibromas). In addition, the “fleshy” mass seems to originate from a single region rather than from multiple body areas; thus, it would fit better with a solitary lesion,¹ as typically occurs with (diffuse) plexiform neurofibromas.^{18,19} For the above reasons, in the absence of other cutaneous stigmata of NF1, we would favour the diagnosis of mosaic/segmental NF1.¹

In patients with mosaic or localised manifestations of NF1, disease features are limited to the affected area, which varies from a narrow strip to one quadrant and occasionally to one half of the body, either in a symmetrical or asymmetrical arrangement.¹ Affected patients may have pigmentary changes (café au lait spots and/or freckling) alone, neurofibromas alone, a combination of neurofibromas and pigmentary changes, or solitary plexiform neurofibromas.^{1,19} In this respect, Aldrovandi’s case would fit with the latter category of isolated plexiform neurofibroma.¹ The accompanying features of short stature, leg asymmetry, and macrodactyly have been previously reported in localised NF1 phenotypes.¹ A solitary (segmental) lesion would actually better explain the lack of other cutaneous NF1 features, rather than an oversight or omission of the portrayer (fig 1) or of Aldrovandi himself (fig 2). Also, the largeness of the mass could be explained by the concept that in mosaic dermatological phenotypes the disease manifestation may be more florid in the affected area.^{1,2} One could also speculate that the short stature and the leg asymmetry (fig 1) might be related to the regional effect of the NF1 gene mutation because body mass and height are often reduced in generalised NF1.^{1,7,24}



Figure 4 The “Human Monsters” from Conrad von Magenberg’s “*Buch der Natur*”, Augsburg, 1475. In the bottom row, the third woman from the left has an elongated sack hanging from the mandible region.

EARLIER ILLUSTRATIONS OF MOSAIC (SEGMENTAL) NEUROFIBROMATOSIS TYPE 1

It is possible to trace other earlier illustrations, though not so scientific, of lesions resembling the solitary plexiform neurofibromas seen in mosaic/segmental NF1. Among the various figures published in “*Des Monstres et Prodiges*” by the famous French surgeon Ambroise Paré (1510-1590) (author of many books on anatomy, surgery, and medicine)¹¹ is that of a monster born on 17 January 1578, in Piedmont, in Chieri, near Turin, Italy (fig 3).^{3,4} The face, writes Paré “...was well proportioned in every way, but there were five horn-like growths from the head along the back” “en maniere d’un chaperon de damoyelle” (“like a woman’s hat”); “...another double fleshy mass like a shirt collar was visible around the neck”. Besides the more or less fantastic deformations (horns, claw-like hands, etc) and relying on the accuracy with which Paré himself reported this case, the fleshy mass hanging down along the back (fig 3) might be diagnosed as a solitary (diffuse) plexiform neurofibroma¹ rather than as a manifestation of generalised NF1, as postulated by other authors.³

The Bavarian naturalist and philosopher Conrad von Magenberg (1309-1374) wrote on theological, historical, and political arguments, but became famous for divulging the scientific knowledge of his day. In his 12th volume of the Augsburg edition of the “*Buch der Natur*” (1350), there is a xylograph (fig 4) which illustrates various types of monsters such as the sciapod with webbed feet, the headless monster



Figure 5 Buffon's girl as painted in the first Italian version (Livorno, 1830) of the "*Histoire Naturelle*" (1749). Personal collection, Marco Giovannini, Paris.

with six arms, the cinocephalus, and the Cyclops, among others. In the bottom row of the xylograph (fig 4), near the bearded woman, can be seen another woman who, according to Choulant,²⁵ has a large goitre and according to Zanca and Zanca¹ "full blown" NF1. In our opinion she appears to have an isolated (diffuse) plexiform neurofibroma (and therefore she would fit the diagnosis of mosaic/segmental NF1)¹ shaped like an elongated sack hanging from the mandible region down to the abdomen.

ANTIQUE ILLUSTRATIONS OF OTHER TYPES OF MOSAICISM IN NEUROFIBROMATOSIS TYPE 1

Other forms of mosaicism in NF1 can be traced in the portraits of "Buffon's girl" of 1749 (fig 5)^{6, 13} and the "Wart Man" of Tilesius (fig 6).¹⁴ In both cases we are confronted by reproductions of severe generalised NF1 phenotypes.

The drawings of the child (fig 5) are by B de Bakker and appeared in Buffon's (1707-1788) "*Histoire Naturelle*" ("Natural History").¹³ Comte Georges Louis Leclerc de Buffon (1707-1788) was a naturalist whose work laid the foundations for advances in the natural sciences in the following centuries. Ten years after becoming the curator of the King's garden in France, he began publishing his 38 volumes which appeared from 1749 to 1788 and were completed posthumously by a further eight volumes edited and printed in 1804 by his assistants.^{3, 4} In a hand painted reproduction of the first Italian edition of the "*Histoire Naturelle*" (Livorno, 1830), the little girl is represented naked, front and back view (fig 5), showing different types of cutaneous anomalies: (1) multiple, dark, leaf shaped areas of hyperpigmentation on the limbs and (to a lesser extent) the trunk; (2) a large, raised lesion with the appearance of "pigskin" encircling the trunk. The anomalies of pigmentation could be compatible with café au lait spots (even though somewhat too raised rather than flat) and the "life jacket" shaped lesions with a diffuse cutaneous plexiform neurofibroma.

The case described in 1793 by W G Tilesius was referred as the "Wart Man".¹⁴ This patient, Johan Gottfried Rheinhard, was reported under the title "Case History of Extraordinary

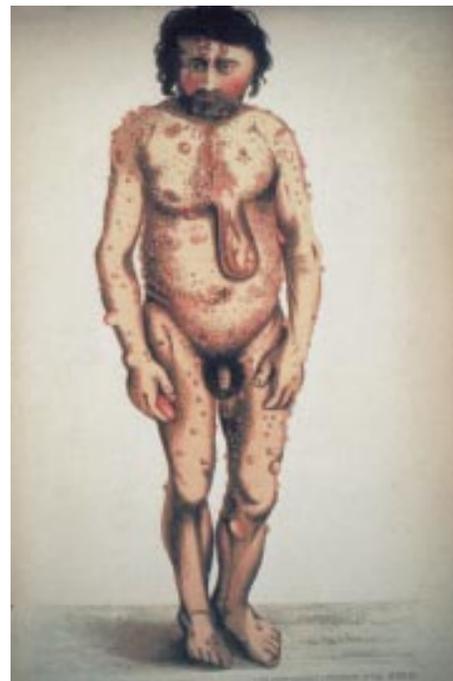


Figure 6 The "Wart Man", Johann Gottfried Rheinhard, as reported by Tilesius von Tilenau, 1793. Authors' personal collection.

Unsightly Skin" and was described as having "countless growths [fibrous tumours] on the skin, café au lait spots, macrocephaly, and scoliosis" (fig 6). In a colour reproduction of the original illustration accompanying the case presentation, one can see a fleshy mass hanging forwards towards the abdomen (fig 6), which might be a pedunculate diffuse cutaneous plexiform neurofibroma.

According to the Happle classification of segmental manifestations of autosomal dominant diseases,² these plexiform neurofibromas of Buffon's girl and the "Wart Man" (figs

5 and 6) could fulfil the clinical criteria for type 2 segmental involvement in NF1 (for example, severe localised manifestations of the disease superimposed on a non-segmental, heterozygous manifestation of the same trait). Taking the description of type 2 mosaicism further, one could speculate that both lesions may reflect loss of heterozygosity for the NF1 gene that occurred at early developmental stages.^{7 19 28–30}

ALTERNATIVE DIAGNOSES FOR ALDROVANDI'S "HOMUNCIO" AND "BUFFON'S GIRL"

Alternative explanations for Aldrovandi's and Buffon's cases could be Proteus syndrome³¹ and phacomatosis pigmentokeratocica,³² respectively. Both these conditions have been explained by autosomal lethal mutations surviving by mosaicism. The underlying autosomal gene is supposed to exert a lethal effect when present in a zygote; the embryo can only survive when the mutant cells are growing in close proximity to normal tissue, that is, in a mosaic state.^{33 34}

According to Proteus syndrome diagnostic criteria,³¹ the Indian "Homuncio" of Aldrovandi could have (fig 1): (1) large connective tissue naevi (or a single large naevus) (if one considers the mass to be composed of connective tissue); (2) disproportionate overgrowth of one limb; (3) disproportionate overgrowth of one digit (macroductyly); and (4) a long face. These findings could explain the multiple distribution of mosaic lesions in different areas of the body in the same person.^{23 31 35} Also, the warmth and redness of part of the mass, reported in Aldrovandi's Latin text (fig 2), could suggest an accompanying capillary malformation within the mass, an additional diagnostic criteria for Proteus syndrome.³¹

The trunk lesions of the girl drawn in Buffon's encyclopaedia (fig 5) could be interpreted as a co-occurrence of speckled lentiginous naevi (the smaller lesions) and/or organoid naevi with sebaceous differentiation (either the macular lesions or the large raised lesion or both) arranged according to Blaschko's lines and distributed in a checkerboard pattern.^{2 32}

We are less in favour of the latter hypotheses because the clinical appearance of the fleshy (fig 1) and flat (fig 5) masses are more similar to the variants of plexiform neurofibroma rather than to the naevi in Proteus syndrome and phacomatosis pigmentokeratocica, respectively.

However, regardless of the diagnostic hypotheses, and relying on the accuracy with which the ancient observers have depicted their cases, these antique illustrations may be considered as remarkable and early examples of mosaicism.

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