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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.
THE INHERITANCE OF CERTAIN HUMAN ABNORMALITIES

BY A. M. GOSSAGE, M.D., OXON., F.R.C.P.

PHYSICIAN TO OUT-PATIENTS AT THE WESTMINSTER HOSPITAL AND THE EAST LONDON HOSPITAL FOR CHILDREN.

The study of Heredity has an absorbing interest for everybody, but to no one should it appeal more than to the physician. From the earliest times he has been prone to regard constitutional inheritance as an important factor in the incidence of disease amongst his patients, and also in the treatment of disease. His facts, however, have in the past been somewhat loosely collected, and naturally the conclusions drawn therefrom have been either vague or unjustified. More scientific methods of investigation have recently arisen in biological research, and have led to important and well-founded deductions in plants, animals, and men. Of these methods, two at present are chiefly employed by biologists. In the first—the statistical method of the biometricians—data of the inheritance of a particular quality are collected from a large number of individuals, collated, and then conclusions drawn. This method has supplied some very valuable results both in animals and man, and by it Professor Karl Pearson and his followers have been able to prove that both physical and mental characteristics are directly inherited from parent to child in a certain definite proportion. For instance, the children of tall parents have more chance of being tall than the children of ordinary people, and this chance can be represented by a definite number. In the same way, clever parents tend to have clever children, and the offspring of the consumptive show a definite tendency to be attacked by phthisis.

The other method of investigation is an experimental one, where individuals exhibiting a certain quality are crossed with others, some possessing the quality and some not, and the proportional representation of the quality is noted amongst the offspring. This method owes its importance to the rediscovery in 1899 of the law which Mendel had been led to enunciate more than thirty years before as a result of his researches on peas. Mendel's law may be roughly stated as follows: certain qualities of living organisms may be arranged in opposing pairs (allelomorphs); both members of an allelomorphic pair may be present in a single organism, being each derived from a separate parent, with the result that the organism as a whole may exhibit only one of these qualities.

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(which is then said to be dominant) or some combination of the pair; both allelomorphs are present in every cell of the organism except in the germ cells or gametes, where the allelomorphs separate from one another, so that each gamete possesses only one member of the pair, and of the total number of gametes half possess one allelomorph and half the other: separate pairs of allelomorphs segregate independently of one another as a rule. In breeding, the fertilized ovum is formed by the union of a male and a female gamete, each of which carries its one allelomorph, and the quality in the offspring depends on the nature of these allelomorphs: e.g. the descendant may have two similar allelomorphs, in which case it would be pure with regard to the particular quality; or two dissimilar ones, as in the instance already given, when it would probably exhibit the quality of the dominant allelomorph, but be impure. This law has been shown to hold good in a very large number of instances in the animal and vegetable kingdoms, and with its aid some very complicated facts of inheritance have been elucidated.

The application of this experimental method to human beings presents many difficulties. To begin with, breeding experiments cannot be arranged, and the investigator is dependent on the haphazard experiments of human marriage. Then the purity or impurity of an individual with regard to a certain quality cannot be ascertained in the absence of progeny, for it is by his children that a man is known. Human families are small, and there is an immense waste of generative cells which are never fertilized. Children are born one at a time, and after the birth of each child the probabilities for a particular combination of germ cells for the next child are not changed by the previous birth. In such small families, therefore, we cannot expect the numbers of the children exhibiting the separate qualities to conform with the theoretical forecast, but when a number of families are grouped together the results ought to approximate to expectancy. The easiest condition to investigate is that of some marked quality, the presence or absence of which is obvious. An example of such a condition is afforded by brown-eyed people who possess pigment in front of the iris, which pigment is absent in the blue-eyed. The brown eye has been shown to be dominant to the blue eye by Hurst, so that brown-eyed children have always one parent with brown eyes, two brown-eyed parents may have a blue-eyed child, but two blue-eyed parents should breed true. Most of the conditions that are easy to investigate are uncommon, consisting of congenital abnormalities, and one observer has thus little chance of meeting more than a few families, and so has to depend for his data on the published observations of others. Unfortunately, in the recording of cases, the heredity factor has been only one of the points on which stress has been laid, and the recorder has often been content with mentioning the number of similar cases in the family, without giving the number of normal individuals. Further, the patients, from whom the facts have to be collected, belong usually to the less intelligent classes, whose memory as to their own children is frequently defective, while it is still more so with regard to the families of their parents and
grandparents. An abnormal child is more likely to be remembered than a normal one, so that an excessive number of abnormal individuals must be expected. In spite of the difficulties, however, the law has been found to hold in a fair number of instances, such as the inheritance of certain congenital abnormalities of the eye, which Nettleship has collected with such care. It becomes, therefore, a matter of interest and importance to investigate the family histories of other abnormalities, and to see how far they correspond with the law.

Certain defects of the skin show a remarkable tendency to be handed down from parent to child, and so promise a fruitful field for investigation. I have myself recently come across a family afflicted with a peculiar horny condition of the palms and soles. This abnormality is a marked one, is apparently always directly handed down from parent to child, and a fair number of affected families have been described, while the family records have been exceptionally well given; here, therefore, is a simple problem for elucidation. The condition is described under a number of names as ichthyosis, Keratosis, Keratoma, or Tylosis of the palms and soles. It consists in an abnormal thickening of the epidermis on the palms of the hands and palmar surface of the fingers, on the soles of the feet and plantar surface of the toes, and the thickening is limited to those parts, not spreading to the dorsal aspects of the hands and feet, and not being found elsewhere over the body. In the vast majority of cases the condition is noticed soon after birth, though occasionally it has not been observed until the age of 5 or 6 (Bohm), but this is so rare that one is almost justified in concluding that the condition was present, but unnoticed, during infancy. In a large number of cases no inconvenience is caused to the affected people, but sometimes painful fissures appear, which may become infected, causing cellulitis and lymphangitis (Deecke), while in other cases the epidermis is shed in the autumn, leaving a tender surface which quickly becomes re-covered by excessively thick epidermis (Crocker). Some recorders have noticed an excessive secretion of sweat in their cases (Thost, and Unna), while others found a diminution of sweat (Deecke, loc. cit.). There seems to be no marked alteration of sensation beyond a slight dulling due to the thickness of the epidermis (Deecke), though Thost says that in his family the feet were so tender that none of the members could walk barefoot. A similar horny condition of the palms and soles may be acquired in adult life from hard work, local irritants, arsenic poisoning, and in association with hyperhidrosis, but this acquired condition is never handed on to the descendants.

Of the family already mentioned, I myself saw two members with this condition. A woman, aged about 45, brought her son, aged 8, to the East London Hospital for Children, as he was suffering from scarlet fever. The palms and soles of both mother and son were found to present a remarkable horny condition of the skin which caused them no inconvenience, and was not associated with excessive sweating or any other peculiarity. In both cases the abnormality had existed from birth. The mother's father and paternal
grandmother had been similarly affected, while her father's sister had been quite normal. Of the woman's own family of 7 children, 2 males and 2 females had a similar condition of the palms and soles, while 3 females were unaffected. In medical literature I have been able to find 45 families afflicted in this way, but closer investigation shows that a number of these families should be eliminated. First come the 5 families described by Neumann from the island of Meleda in the Adriatic. In consequence of these cases, the condition here described has often been called the mal de Meleda, but, as Vorner has pointed out, Neumann's cases differ clinically from tylosis palmaris et plantaris in that the horny condition affected the backs of the hands and feet, and other parts of the body. As the mode of inheritance is also different, for the affected individuals were generally born of unaffected parents, we are justified in excluding his cases. A complete study of the mal de Meleda from the hereditary point of view would be of great interest and value; at present the reported cases are too few and too incomplete for any conclusion to be formed. The family described by Sümberger should also be omitted, as the abnormality did not appear until the age of 8, and only the feet and not the hands were affected. The condition in this family was directly handed on from parent to child, but a very small proportion were sufferers. The patient's father and grandfather suffered, but his 12 brothers and sisters were quite free.

This reduces the number of families to 39, and of these 10 are so incompletely reported, or consist of so few members, that they are of small value for our purposes. Another family, that reported by Ballantyne, has also to be put on one side, for reasons that will be mentioned presently. Examining the records of all the 39 families, it is found that the condition is handed down directly from parent to child, that it equally affects males and females (166 males to 140 females), and that it is transmitted equally through males and females (66 males transmitted the condition to some of their offspring, and 52 females). These characteristics suggest that the abnormal condition is dominant to the normal. Owing to the fact that the
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affected people are constantly crossed with normal; none of them would be pure dominants that is to say, they all contain one of the dominant alleles. 

On sexual intercourse taking place with a normal individual, half the gametes of such an abnormal person will contain the dominant allele, and half the recessive, whereas all the gametes of the male will be recessive. It is an even chance, therefore, whether an individual gamete of the normal mate will be impregnated by a normal or an abnormal gamete, and if a number of children...
ception. We are justified, therefore, in regarding tylosis of the palms and soles as a dominant Mendelian allelomorph to the normal condition.

It has been pointed out that these abnormal individuals are none of them pure dominants. Pure dominants would be expected to arise from the conjunction of two such abnormal persons, in the proportion of 1 pure dominant, 2 impure dominants, and 1 recessive, but there is no record of any intermarriage of this kind. The only other way in which we can imagine pure dominants to arise is by a marked mutation de novo. A pure dominant should transmit to all his children, since every recessive gamete would be impregnated by a dominant gamete, and all the offspring would be impure dominants. It is interesting to note that in the two cases where the condition definitely started de novo, both parents being normal (Jacobi), all the descendents of the abnormal persons were similarly affected. The numbers of such further offspring are too small however, to warrant any conclusions being drawn, being 2 in

![Diagram](image)

**Fig. 3. Tylosis palmaris et plantaris. Jacob and Fulton's family.**

Jacobi's case and only 1 in Schotz's case. In the family reported by Jacob and Fulton, the affection is somewhat definitely stated to have first appeared in a woman whose mother accounted for her baby's condition by having gazed intently at some fish while pregnant. It is possible, therefore, that this was a case arising de novo, and it is noticeable that all her 12 children were affected. (See Fig. 3.)

There is one family (Ballantyne) which is not in agreement with the view put forward here, since the condition, which had existed in the family for generations, was said to affect only the females and to usually skip a generation. The patient's mother was said to be normal, but the patient transmitted the abnormality to her daughter, while her son was unaffected. This patient may have been mistaken, or possibly some other factor is necessary
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for the condition to show itself, such factor being only very rarely absent from normal people. In two other instances it seemed possible that a generation was skipped in the inheritance. In Horton Dale's family, the brother of the original patient had an affected child, while nothing is said about the brother himself; Vorner concludes that he was not affected, but Ballantyne, writing much nearer the time of Dale's paper, definitely says that he was affected; so that we may conclude that a generation was not skipped. The report of Ehrmann's case leaves a doubt as to whether the mother of the patient was or was not affected, but Prof. Ehrmann has kindly informed me that there is a misprint in this report, which should read: 'In der Familie ist dieselbe Erscheinung beim Urgrossvater, der Grossmutter, der Mutter, bei 6 Brüdern der Mutter und 3 Schwestern der Patientin vorhanden; 4 Schwestern der Mutter und 1 Bruder der Patientin sind davon verschont.' Ballantyne's family,

![Diagram](image)

**Fig. 4.** *Epidermolysis bullosa.* Bonajuti's family.

therefore, is the only one where a generation is skipped, and as the affected and unaffected are approximately equal in the families of the affected we may be certain that the opposing allelomorphs are equally divided among the gametes.

Inheritance is the most important factor in a number of other peculiarities of the skin, but in many of these the families are too few and too small for any definite conclusions to be formed. As a rule, the abnormal condition seems to be dominant to the normal (Waelch, Colcotte Fox, and Wilson). The condition of multiple hereditary telangiectasis seems also to be a dominant to the normal condition. Unfortunately, the family histories in this interesting complaint are not very full, the normal individuals being evidently left out in many of them. In three instances there are fairly full records (Wickham Legg, Parkes Weber, and Kelly), and in these the numbers are: affected 14,
and unaffected 27. It has to be remembered that the complaint does not show itself in early life, and that many of the children therefore die young, before an opportunity has been afforded for ascertaining whether they were really free from the family complaint. This, no doubt, gives a partial reason for the great excess of the unaffected. There is, too, a probability that in Parkes Weber's family the condition had been handed down through an unaffected individual.

Dr. Walter Bell, of Lowestoft, has kindly sent me a record of a family in which tightly curled, short, woolly hair of the negro type tended to occur, although the features were not in the least negroid. A tradition in the family attributes the peculiar hair to a 'Mexican' ancestor several generations back. The peculiarity was transmitted directly, was found in both males and females, and half the children of the affected had the abnormal hair (18 affected to 18 free). See Fig. 5. Rizzoli (quoted by Stricker) gives a remarkable family history of the inheritance of a tuft of congenitally white hair over the brow through six generations. This was handed down directly from parent to child, and of the progeny of the affected 15 were also affected, and 15 free. See Fig. 10. Morgan and Godlee give records of a similar inheritance of a tuft of white hair in each family through four generations, where the inheritance was direct from parent to child. Unfortunately, neither of them say anything about the unaffected members of their families. This abnormality of the hair, as well as that described by Dr. Bell, seems to be a simple dominant.

Some very remarkable family histories have been published concerning the condition to which Köbner gave the name of Epidermolyosis Bullosa. This is essentially a congenital abnormality of the skin which shows itself soon after birth in a peculiar response to slight irritation, by the formation of bullae
filled with clear serum. Hallopeau distinguishes two forms: one with merely the eruption of bullae and no subsequent trophic changes (though Herzfeld noticed alterations of the nails), and the other with marked trophic changes in the nails, and scarring and atrophy of the skin after the bullae; miliary cysts, containing broken-down epithelium, tending to develop after the disappearance of the bullae in the latter form. The two forms are evidently closely connected and give similar family histories, and so may be considered together. The seats of selection for the bullae are the hands, soles, knees, and elbows, but they may form anywhere, even in the mucous membrane of the mouth. The records of these cases show certain striking differences from those of tylosis of the palms and soles. There are, for instance, a very much larger number of cases in which heredity apparently plays no part, and a much larger number of cases whose parents were quite healthy. The skipping of a generation, too, is a comparatively frequent occurrence in the family histories (ep. Bonajuti, Colombini, and Török). In the majority of cases, however, the condition is directly inherited, affects males and females alike, is transmitted equally through males and females, and attacks about half the progeny of those capable of transmitting it (180 affected to 209 unaffected, in 27 families). It is noticeable that the expected excess of affected is not found, the reason evidently being that some of the unaffected are capable of transmitting the condition to their offspring and so should be included amongst the affected. We are, however, justified in concluding that the opposing allelomorphs are divided equally amongst the gametes.

Examples of heredity of a similar character to that in epidermolysis bullosa have been met with in both animals and plants, and the reason of the capability of some of the unaffected to transmit has been worked out experimentally in several instances. It is, for instance, possible that the dominant allelomorph may occasionally not show itself, though present, as appears to occur with extra toes in fowls (Bateson), or it may be necessary for the exhibition of a particular characteristic that two factors should be present together; or again, an inhibiting factor may be present in individuals who would be expected to exhibit the characteristic but do not do so. It would be attractive to speculate on the explanation of the heredity in epidermolysis bullosa and other similar conditions in human beings, but, in the absence of the proper conditions of experimental research, the explanation would be pure speculation and incapable of proof.

The family records of xanthoma give somewhat similar results to epidermolysis bullosa. This condition is characterized by the appearance of yellow patches on the eyelids, and sometimes by the eruption of yellowish papules all over the body. The two forms may be conjoined, or may occur separately. They most commonly occur sporadically in association with jaundice, but both forms may be inherited. When inherited, the first appearance may take place in early childhood, or may be delayed until puberty, these peculiarities being characteristic of the particular families in which they occur; i.e. early appear-
ance in one family, late in another. There are 7 families sufficiently fully
given for conclusions to be drawn, and the numbers come out 34 affected to 35
unaffected. The condition is sometimes transmitted through the unaffected (cp.
Török and Church).

A tendency to early baldness, with the development of moniliform hairs,
monilithrix, also tends to occur in families. The number of families recorded are
few, only 5, and 2 of these (Hallopeau and Lefèvre; Beatty and Scott) are
evidently incomplete. In the other 3 families the number of affected is 31, and of
the unaffected 30. There seems a definite skipping of a generation in Beatty
and Scott's family, so that this condition is very similar to epidermolysis
bullosa.

Hypotrichosis congenita familiaris is an affection where children are born
without hair, or in which the hair disappears in the first few months of life, never
to reappear. This affection is recorded as appearing in 7 families, and, as in the
other conditions described, appears to be dominant to the normal. In these
families there were 26 affected and only 10 free, but it is evident that in several
of the families the normal individuals have not been mentioned. Since several
affected children in one family have been born to healthy parents, it is probable
that the inheritance of this affection is similar to that of epidermolysis bullosa.

Similar family histories are afforded by the cases of enlarged spleen, quoted
by Cowan in the Quarterly Journal of Medicine. Here the affected are 21
and the unaffected 42, the great excess of the latter being probably partly
explainable by the large number of children who died in infancy before they had
an opportunity of developing the family complaint. In these families a genera-
tion seems to be sometimes missed, and on several occasions more than one
affected child has resulted from the union of healthy parents.

The condition of polyuria and polydipsia, to which the name of diabetes
insipidus has been given, is again of a similar character when it is hereditary.
Gabriel Pain's family is too incomplete for use, there being no mention of the
normal members, and the families reported by Lacombe and Orsi are probably
also incomplete, but have been included. In the 4 families which I have grouped
together there were 43 affected to 50 unaffected. In Gee's family there are 3
instances of a generation being missed, the abnormality appearing again in the
grandchildren.

In 1893 a peculiar and hitherto unknown skin affection was independently
described by Mibelli and Respighi as occurring in the province of Parma in Italy,
and they occasionally described the same cases. In this condition a raised horny
ridge appeared on the skin, which spread centrifugally while the centre became
depressed, and was characterized by atrophy of the constituents of the skin.
Mibelli called the condition Porokeratosis, believing that it started from the
sweat glands, while Respighi denied this, and proposed the name Hyperkeratose
figurée centrifuge atrophiant. Several further cases were recorded, and in most
of them it was found that the condition was a family peculiarity. The trans-
mission was always direct from parent to child, and, so far, no case of a generation
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being skipped has been recorded. On several occasions, however, more than one member of a family has been affected while both parents were quite healthy. It is noticeable that the number of unaffected is much higher than in the other conditions which have been considered, there being 72 unaffected to 48 affected in 10 families. It must, however, be remembered that the affection first appears in adult life, and that several who might have been affected had died young, before the condition had had time to develop. This explanation, however, will not hold in the case of a family, the record of which has been kindly sent me by Dr. Walter Bell. In this family, heterochromia of the iris tended to appear when one eye, always the left, was "greyish blue in colour, with chestnut-

![Diagram of Dr. Walter Bell's family]

Fig. 6. *Heterochromia of iris*. Dr. Walter Bell's family.

brown patches'. Of the offspring of the affected members of the family, 8 were affected and 22 free. (See Fig. 6.)

General ichthyosis and ichthyosis follicularis both tend to occur in families, but it is difficult to bring the records into line with one another. For instance, Byron Bramwell, in one family with ichthyosis, finds the condition directly transmitted to 3 out of 5 of the children of an affected person, while in another family there was a tendency to the sporadic occurrence of ichthyosis without the parents of the sufferers being affected. Again, ichthyosis is said to often occur in several members of a family without there being any hereditary influence (cp. for instance, Gaston). Lameris and Bond both describe families in which it occurred only in the males, but was handed down through unaffected females. I have myself recently come across a family several members of which suffered from general ichthyosis. In the diagram of this family, given in Fig. 8, it will be seen that the condition has been handed down from an affected grandfather to 2 out of 6 grandchildren, through an unaffected son.

In the various families that have been considered in this article, there tends
to be an equality between normal and abnormal in the offspring of abnormal individuals, and the abnormality tends to be handed down directly from parent to child (though to this there are a number of exceptions), and we are, therefore, justified in concluding that the inheritance is conducted on Mendelian lines, the abnormality being a dominant allelomorph to the normal. In cases such as porokeratosis or multiple teleangiectasis, where there is a large excess of the apparently normal in the offspring, it is not improbable that this excess is to some extent only apparent, owing to a number of individuals dying before the period of life when the abnormality shows itself, a proportion of such prematurely dead persons really having the family abnormality. The number of families here considered is, unfortunately, very small, and for the satisfactory proving that heredity may be of this Mendelian type a very much larger number is required.
The facts are however suggestive, and we may hope that future records may firmly establish this explanation, especially if these records are more complete than those at present available. Our profession should now recognize that in the

study of these family complaints the normal individuals are quite as important as the abnormal, and that it is advisable that as many members as possible of the family should be personally examined. The heredity in the families con-

sidered seems to be of a comparatively simple character, the abnormal condition being dominant to the normal, but in other families one must expect a more complicated problem. For instance, the abnormality may be recessive to the
normal condition when it would be expected to show itself, especially in the offspring resulting from the marriages of cousins. Again, the condition may be limited to one sex, as appears to be partly the case with haemophilia. Accurate and full records of as many families as possible are required for the elucidation of all these problems.

In conclusion, I have to express my thanks to Dr. Colcott Fox, who greatly facilitated the task of searching through the literature by lending me his notebooks, to Dr. Graham Little for getting details of a family translated from a Russian periodical, and to Mr. Bateson for constant help and criticism.

A few diagrams are appended, illustrative of family histories. In those the affected individuals are black, the normal ones white, and the sex, where known, is indicated in the usual way. The individuals are not placed in these diagrams in the order of primogeniture. A number of normal persons is indicated by a numeral in a large circle. In the references the numbers of affected and unaffected individuals in each family are given. A black spot being placed at the top of the columns of the affected, and a white one at the top of the unaffected.

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7 families

Compare also:
Gendre, Thèse de Paris, 1880.
Hutchinson, Archives of Surgery, Lond., lxxiv, 1894.
Wilks, Trans. of Path. Soc., Lond., xix, 446.

Enlarged spleen: quoted by Cowan, Quarterly Journal of Medicine, Oxford, 1907, i, 11

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5 families

Hypotrichosis congenita familiaris

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<td>i, 347</td>
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<td>Singer, Monatsch f. prakt. Derm.</td>
<td>Hamburg and Leipzig, 1907</td>
<td>xlvii, 442</td>
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6 families

Monilithrix

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3 families

Compare also:
**THE INHERITANCE OF CERTAIN HUMAN ABNORMALITIES**

**Diabetes insipidus**
- Geo. St. Bart. Hospital Reports, Lond., 1877, 79
- Lacombe, Jour. de med. et chirur., 1841, 309
- Orsi, Gaz. med. Lomb., xxxvi, 1881, quoted by Weil
- Weil, Virchow's Archiv, Berlin, xv, 1884, 70

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Compare also:

**Porokeratosis**
- Ducrey and Respighi, Ann. de derm., Paris, 1898, 609
- " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " " 
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- Gilchrist, Jour. of Cut. and Genito-urinary Diseases, New York, 1899, 119
- Mibelli, Monatsch f. prakt. Derm., Hamburg and Leipzig, xvii, 1893, 47
- Mibelli, Archiv f. Derm. u. Syph., Wien, 1899, xlvi, 1
- Mibelli, Ann. de Derm. et Syph., Wien, 1905, 504
- Reisner, Inaugural-Dissertation, Strassburg, 1896
- Respighi, Giorn. ital. delle mal. ven. e della pelle, 1893

| Source | Comments | 7 | 12 | 3 | 11 | 3 | 11 | 5 | 12 | 11 | 4 | 6 | 2 | 6 | 3 | 4 | 10 families | 48 | 72 |
|--------|----------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|-------------|----|----|

Compare also: