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Tylosis Associated with Carcinoma of the Oesophagus and Oral Leukoplakia in a Large Liverpool Family—A Review of Six Generations

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INTRODUCTION

TYLOSIS HAS been classified by Cockayne [1] as one of the many types of dyskeratosis. The condition is readily identifiable as a thickening on the areas exposed to pressure and/or friction, as seen on the skin of the palms and soles (Fig. 1). In a number of these patients a horny epidermis is shed at intervals leaving a tender red surface which is quickly overgrown again. At a microscopic level there is general hypertrophy of all the layers of the skin but the epidermis is mainly affected. There are several types of inherited tylosis, Type 'A' which has a later age of onset (5–15 years); type 'B' which may be diagnosed in the first year of life [2]. The late onset tylosis families are associated with oesophageal cancer.

The association between tylosis (palmoplantar keratoderma) and oesophageal carcinoma in a group of related patients was initially reported in these large Liverpool families by Clarke and McConnell [3]; Clarke *et al.* [4] and Howel-Evans *et al.* [5] and subsequently in other British, Spanish, Indian and American families [6–11].

Abnormalities of the oral mucosa in the tylotic patients have been described by Tyldesley and Osborne-Hughes [12] and Tyldesley [13]. The oral lesions have been described as a pre-leukoplakia which presents in childhood and has both clinical and histological characteristics similar to other oral epithelial disorders [12]. It was suggested by these authors that oral leukoplakia associated with tylosis should be considered as a possible indication of a tendency to develop oesophageal carcinoma.

In Liverpool the tylotic family 'S' [5] has been studied over six generations with 345 individuals and to-date 57 have died (Fig. 2). 32 of the deceased patients were tylotic and 21 (66%) have died of oesophageal cancer. The family pedigree is compatible with autosomal dominant inheritance [5]. The possibility that tylosis and the development of oesophageal carcinoma are controlled by a single locus has been considered and is supported by the apparent lack of recombination in the family. None of the non-tylotic members of the family have died of oesophageal cancer.

The purpose of this review is to record the developments that have taken place in the largest of the Liverpool tylotic families since the publications of Howel-Evans *et al.* [5] and Harper *et al.* [4] and to report on new cases of carcinoma of the

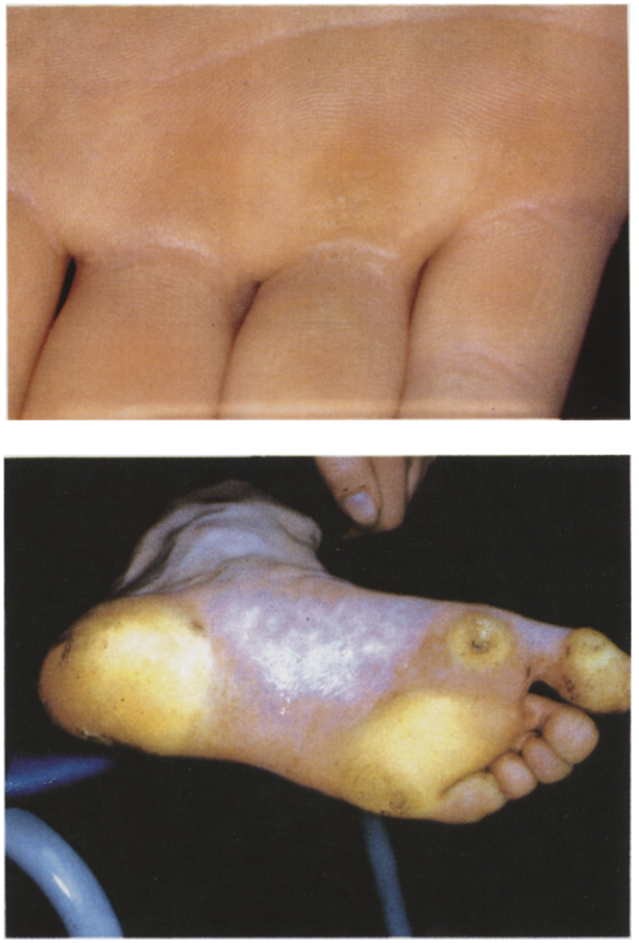

Fig. 1. Clinical appearance of tylotic lesions on hands and feet. Patient V74 aged 15 with tylotic lesions on (upper panel) hands, (lower panel) feet.

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Table 1. *Tylotic patients with oesophageal cancer* 1969–1993

Pedigree	Sex	Age at death	Comments in Howel-Evans *et al.*, 1958
III 31	F	66	Alive aged 57 examined
III 54	F	62	Unaffected, aged 33 examined
III 56	M	63*	Not traced
IV 17	F	A	Examined aged 22
IV 53	F	53	Examined aged 25
IV 57	F	A	Examined aged 14
V 4	M	50	Examined aged 11 clear evidence of tylosis
V 68	M	23	Not seen

*Patient had oesphageal cancer but died of unrelated bronchial disease.

oesophagus associated with tylosis. The significance of this family in determining the 'Tylosis Cancer Gene' (TCG) is discussed in the light of the recent molecular techniques that are now available to identify candidate genes associated with genetically inherited diseases.

FOLLOW-UP OF FAMILY 'S' OVER SIX GENERATIONS

Family 'S' is the largest of the Tylotic families that were originally reported in the Liverpool area [2, 5]. Members of this family have been followed-up by home visits and a proportion of the 'at risk' individuals have periodically attended the Department of Gastroenterology at Broadgreen Hospital, Liverpool for oesophagoscopy. All consenting members of this family living in Britain who had not been examined prior to 1970 and the younger members of this family have been examined for clinical signs of tylosis. Deaths within this family were noted for both the tylotic and non-tylotic members and verified from death certificates and clinical records where possible.

FAMILY 'S' PEDIGREE

The pedigree of this family contains 345 individuals and has grown considerably since the last update of the original pedigree in 1970. Since that time a further eight members of the family have developed oesophageal cancer of whom five have died of the disease and one died of an unrelated bronchial disease (Table 1).

The pedigree has been updated and due to its increased size it has now been divided into six sub-families (Fig. 2). A number of the sub-families have not been updated into the V and VI generations, either because there was no tylotic trait within that part of the family or because the family has left the area and has therefore been lost to follow-up.

ASSOCIATION OF TYLOSIS WITH OESOPHAGEAL CARCINOMA

Eighty-nine individuals in the Liverpool 'S' tylosis family have been diagnosed as tylotic, of whom 57 are still alive. A total of 21 tylotic members of this family have died of oesophageal neoplasia and 11 have died of other causes (Table 2). In the past 18 months, 3 patients have been identified with severe dysplasia through the oesophageal screening survey programme and have undergone surgery, 2 of whom are alive and the third person died 6 months post-operatively from the disease. The fate of all 25 tylotic members of family 'S' with oesophageal cancer is shown in Table 3 with the site of an oesophageal neoplasm. The majority [12] had cancer in the lower third, eight in the mid third and two in the upper third of the oesophagus. It is of note that patient III 54 was reported in the 1958 paper by Howel-Evans *et al.* [5] as 'unaffected' at the age of 33 but was subsequently diagnosed as tylotic in her late thirties prior to her developing carcinoma of the oesophagus at the age of 52.

Patient III 53 received surgery for an oesophageal carcinoma in 1956 but recently (1992) underwent surgery for an oral carcinoma. He was the first member of the family to develop a cancer in the head and neck region. He was examined in 1979 and found to have a very markedly speckled leukoplakia in the angular fissure on the right-hand side of the mouth. He refused treatment at that time but developed a squamous cell carcinoma in the same region of the lip and on the right buccal mucosa in 1991. The patient was known to have a history of heavy smoking and drinking, factors which have been specifically linked to the overexpression of the p53 tumour suppressor gene in patients' with head and neck cancer [Field *et al.*, 14, 15]. The association therefore between the oesophageal and oral carcinoma may be only a coincidental finding.

The details of all the 25 non-tylotic deaths in this family have been documented in all but 5 cases. 3 of these individuals have died of a cancer of either the trachea, bowel or bronchus, however, none died of cancer of the oesophagus (Table 4).

Early onset (type B) tylosis has not been associated with any serious disease and has been reported by a number of investigators [2, 16, 17]. In contrast the late onset tylosis families reported by Howel-Evans *et al.* [5] (families 'S' and 'C') and Harper *et al.* [2] (families 'G' and 'H'), were all associated with oesophageal carcinomas. However, Ritter and Peterson [18] reported a tylotic family in the U.S.A. in which the one individual who had oesophageal cancer was classified as 'early onset' tylosis. In addition a report from India on a tylotic family with 22 affected individuals, spanning over five generations, were all affected at birth [8]. However, only one individual developed oesophageal carcinoma in this group. He also had a previous carcinoma of the skin. Two other tylotic members of this Indian family also developed squamous carcinomas of the skin. These authors suggested that 'genetic tylosis' may be considered as a precancerous dermatosis. However, a genetic link between tylosis and the development of oesophageal cancer in this family is very tenuous. A further two tylotic families have been reported in Spain from villages 15 miles apart but have no known family connections [10]. In these families, 6 patients with keratoderma also presented with precancerous and cancerous conditions of the oesophagus or stomach. Shine and Allison [6] reported on an association between tylosis and oesophageal pathology, in which the tylosis trait was associated with congenital oesophageal abnormalities over three generations. This latter tylotic family represents a completely different situation from that reported in the Liverpool patients.

ORAL LEUKOPLAKIA AND TYLOSIS

16 out of 17 adult tylotic patients were reported by Tyldesley [13] to have lesions of the oral mucosa, 16 of whom were members of the 'S' family. The lesions were described as leukoplakia and also had associated areas resembling that of

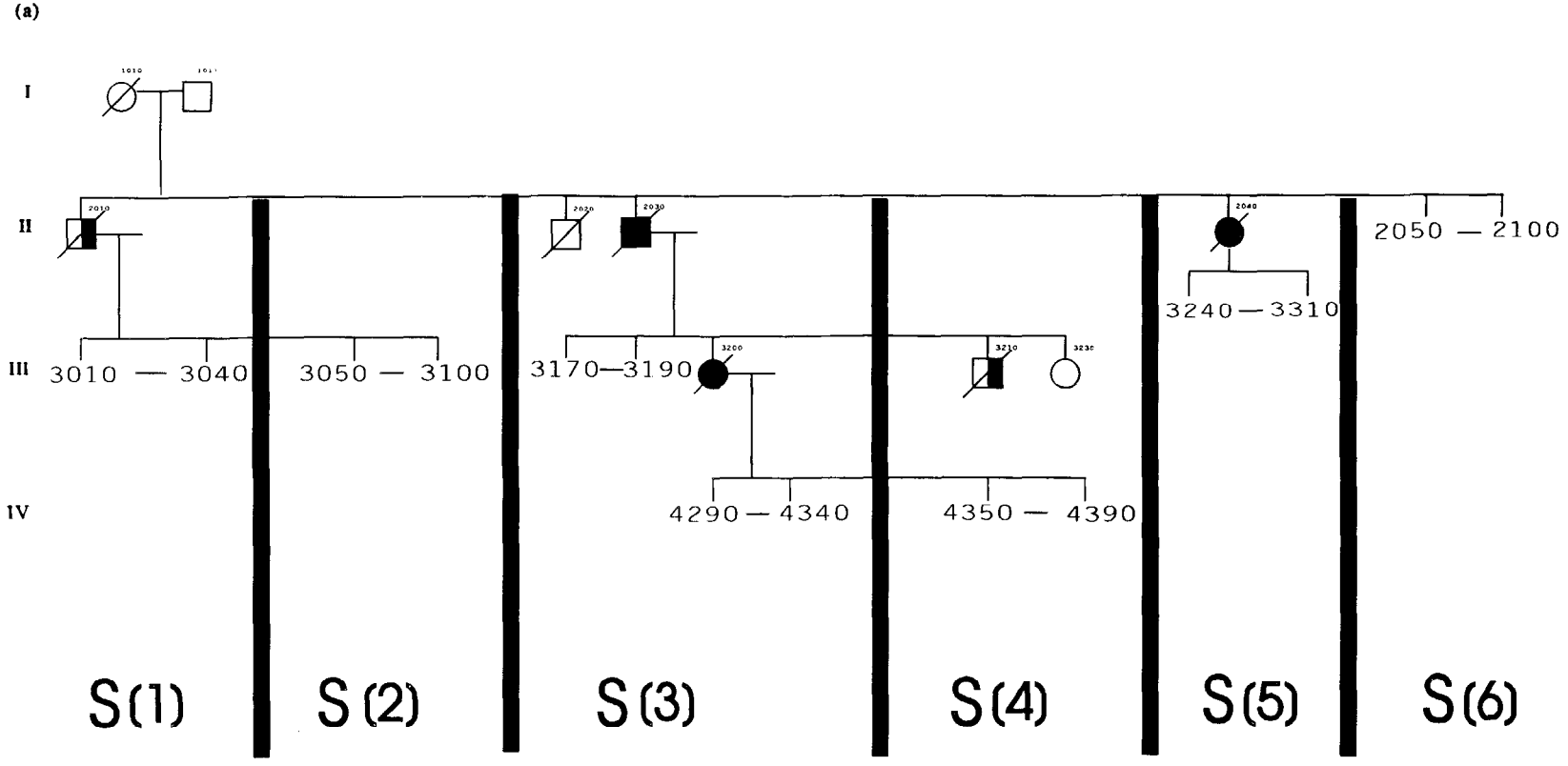
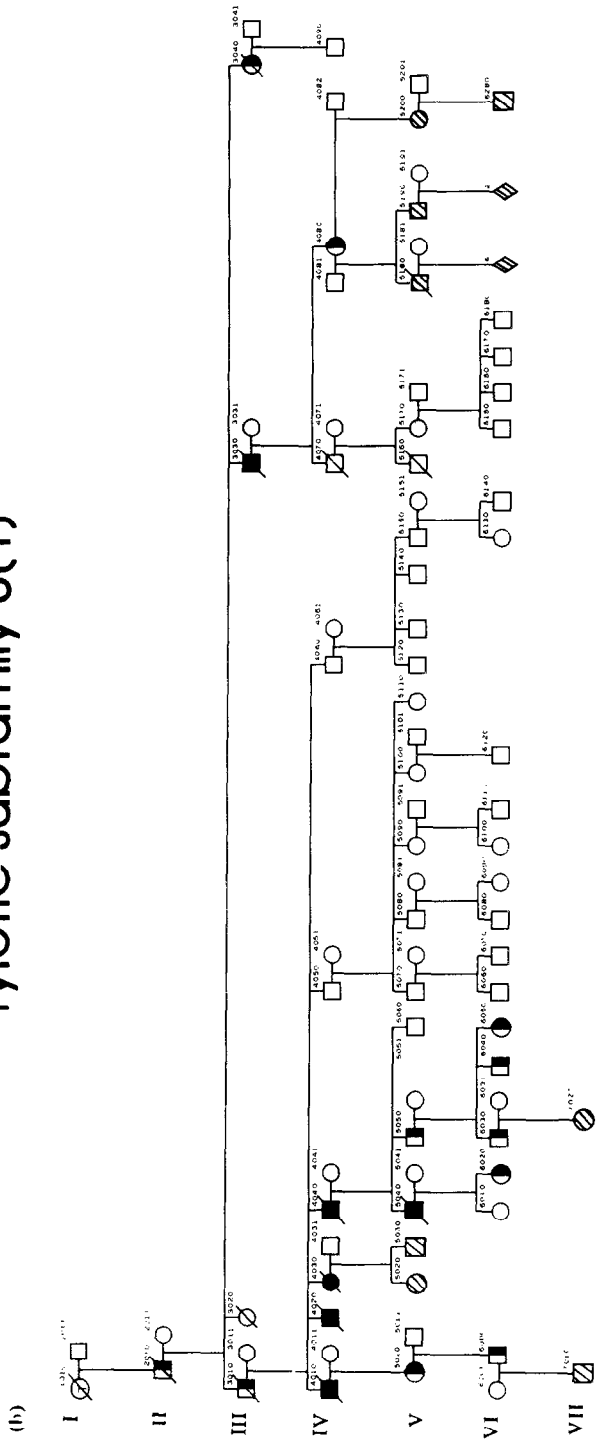
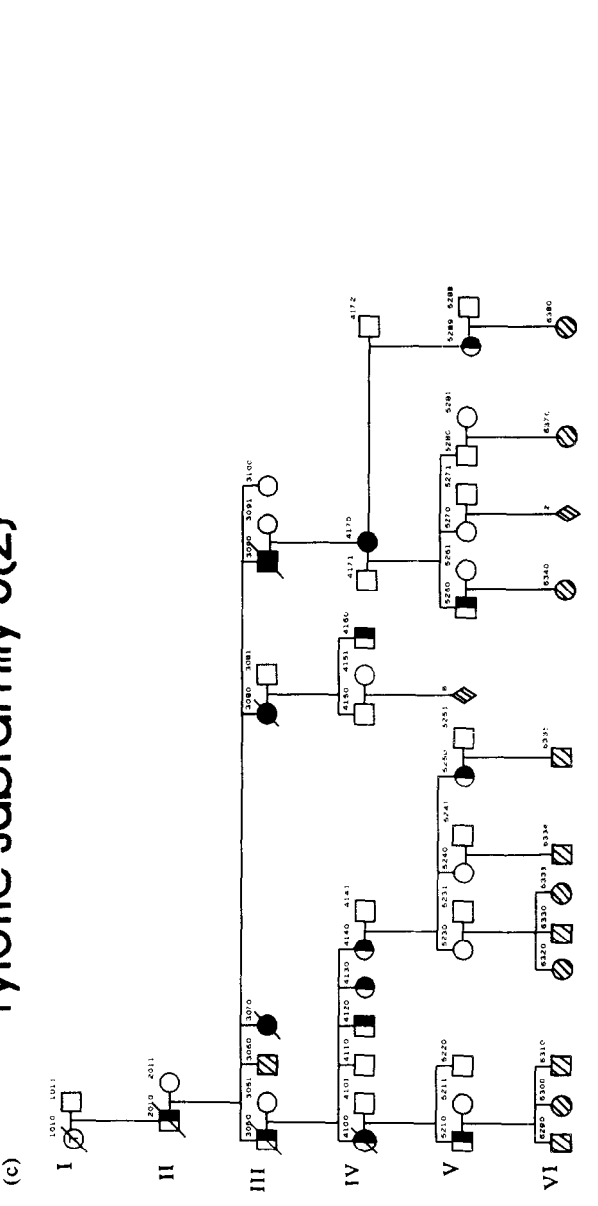


Fig. 2(a–g). Pedigree of the tylotic family 'S' in Liverpool 1993. The pedigree was drawn up using *Megabase* 'A clinical and linkage database' written by Dr I. Fenton, Department of Genetics, University of Wales. The 'S' tylotic family now has over 340 family members over six generations. In order that the pedigree may be used for future reference it has been split up into six legible sub-families $S_{[1]}$–$S_{[6]}$ (Fig. 2b–g). Figure 2(a) indicates the way the family has been subdivided. The nomenclature system used for each individual in this paper has been adapted from that original devised by Howel-Evans *et al.* [5], but maintains the original identity of each individual within each new number. The computerised pedigree system demands an individual number for each person in the pedigree, thus the first digit of each number indicates the 'generation number' and the last number indicates if the individual is a 'blood relative' of the 'S' tylotic family, (i.e. 0) or a spouse of the tylotic member (i.e. 1). The digits between the generation number (first number) and the spouse number (last number) represents the 'Tylotic patient number' as used in Howel-Evans *et al.* [5].

i.e. 1010 = Generation 1, individual 1 (I1 nomenclature used by Howel-Evans *et al.* [5])
1011 = generation 1, spouse of individual 1.

In certain instances new members of the family have been identified and added to the pedigree after the original generation was numbered. In order to keep the same numerical system, the extra individuals have been given a specific recognition number; i.e. 5289. Spouses of the 'S' family members have not been identified as alive or dead. ⌀ Determined from medical history, □ unaffected male, ○ unaffected female, ◑ affected female, ◨ affected male, ∅ dead female, ◇ number of unaffected children, ⊘ too young to show trait or trait to be determined, ■ tylosis and oesophageal cancer.





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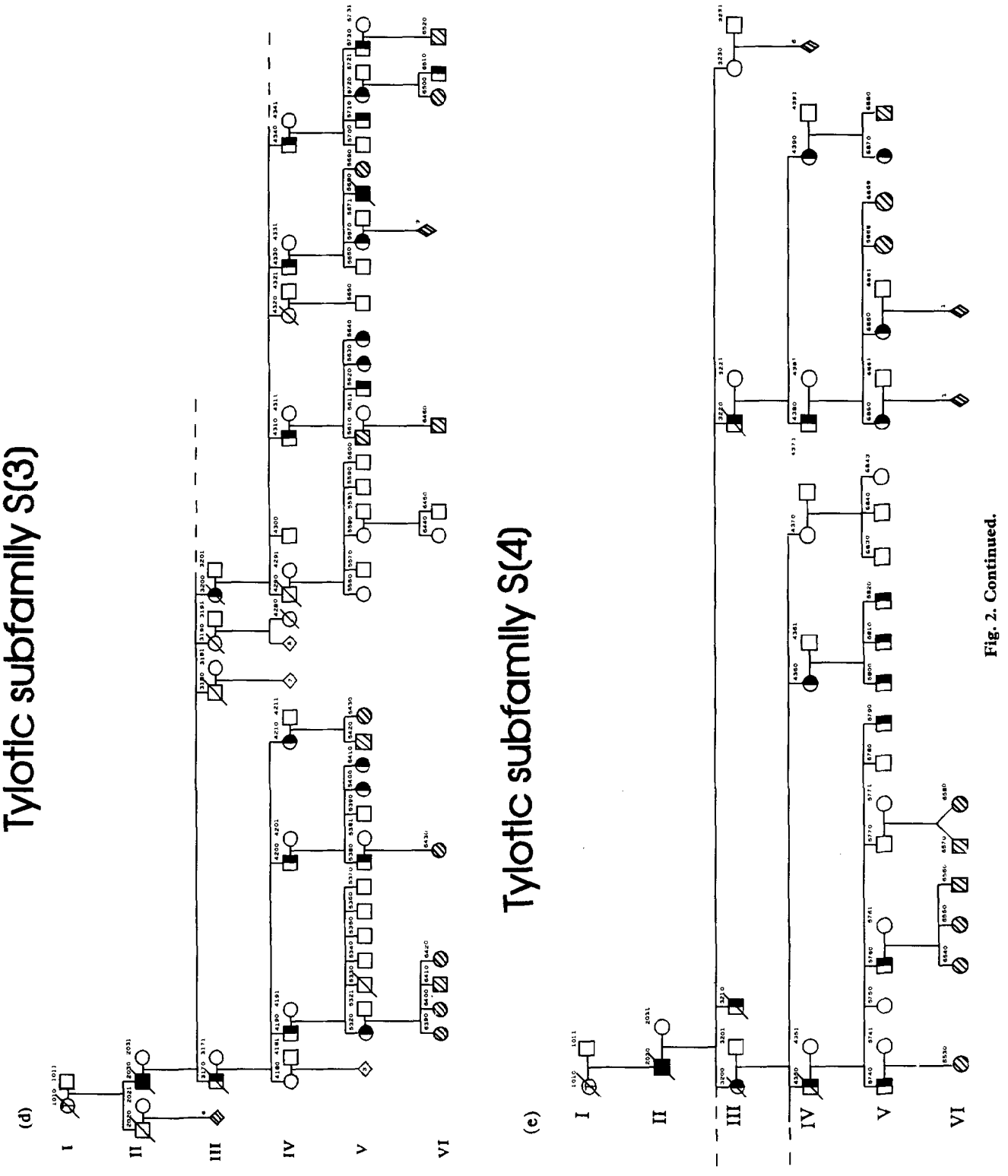

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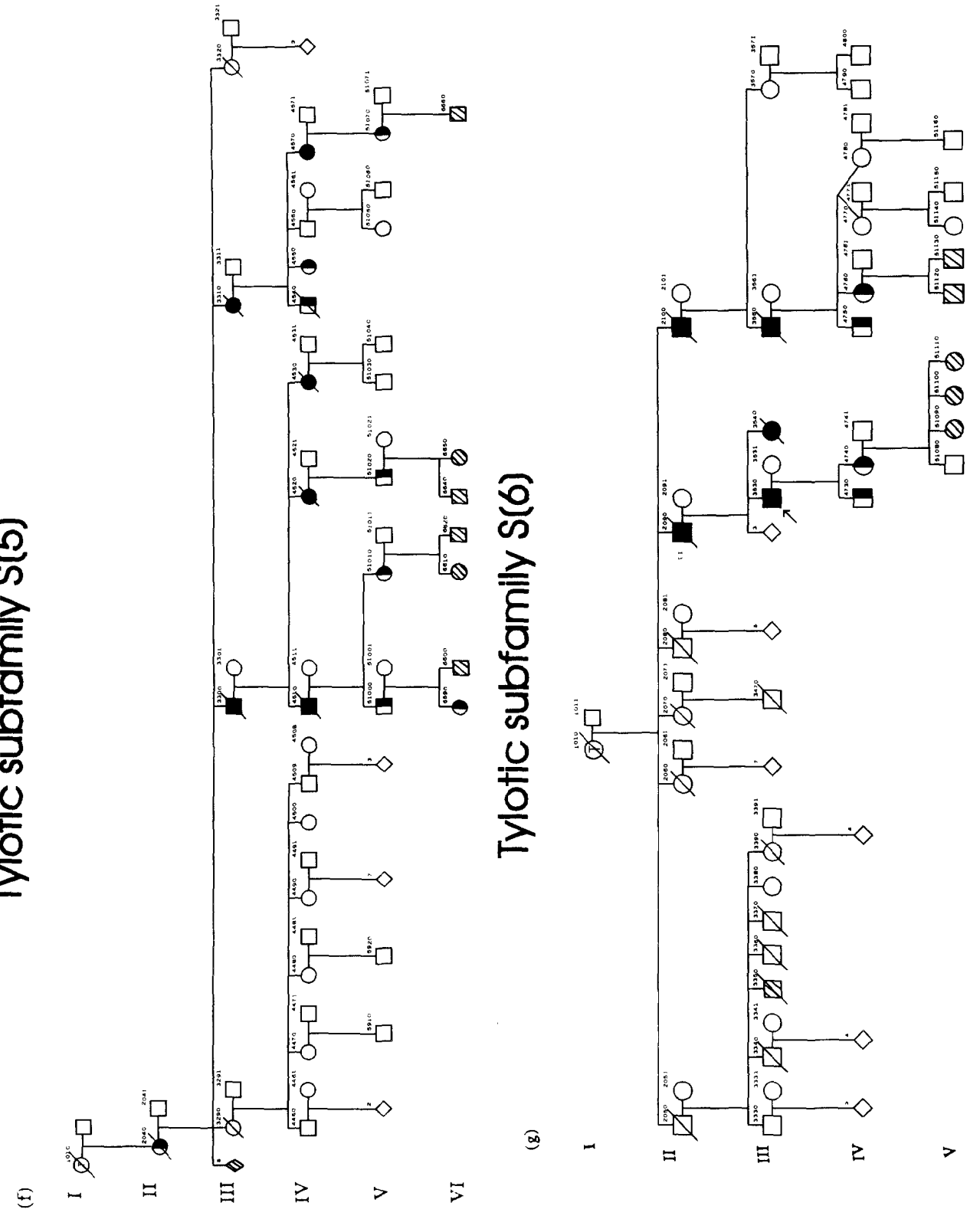

Fig. 2. Continued.

Table 2. *Cancers and other deaths in members of the 'S' tylotic family*

	Dead tylotic		Live tylotic	
Cancer	No.	Patients	No.	Patients
Oesophagus	22*		3	III 53, IV 17, IV 57
Oropharynx			1	III 53
Stomach	1	III 1		
Breast			1	IV 14
Cardio/respiratory	2	III 17, III 22		
Neuro/psychiatric	3	III 20, IV 10, IV 35		
TB	1	III 21		
Renal	1	IV 54		
Cause unknown	2	II 1, II 4		
Total	32			

*II 3, 9, 10
III 3, 4, 5, 7, 18, 19, 30, 31, 54, 56†
IV 1, 2, 3, 4, 51, 52, 53
V 4, 68
†III 56 patient had oesophageal cancer but died of an unrelated bronchial disease.

Table 3. Fate of tylotic 'S' family patients with oesophageal cancer and site of the neoplasm

'S' family	Sex	Age Death	Age Alive	Site
II 3	M	46		N/K
II 9	M	63		Lower third
II 10	M	45		Lower third
III 3	F	70		Lower third
III 4	F	63		Mid third
III 5	M	46		Lower third
III 7	F	52		Lower third
III 8	F	43		Lower third
III 9	M	62		Mid third
III 30	M	65		Lower third
III 31	F	66		Mid third
III 53	M		68	Lower third
III 54	F	62		Lower third
III 56	M	63*		Mid third
IV 1	M	43		Mid third
IV 2	M	49		Mid third
IV 3	F	37		Mid third
IV 4	M	44		Lower third
IV 17	F		57	Upper third
IV 51	M	34		Mid third
IV 52	F	40		Upper third
IV 53	F	53		Mid/Lower third
IV 57	F		50	Mid/Lower third
V 4	M	50		Lower third
V 68	M	23		Lower third

*Death not due to carcinoma of the oesophagus, died of unrelated disease.

Table 4. Causes of death in the non-tylotic members of the 'S' family

	No.	Patients
Non-oesophageal carcinomas		
Trachea SCC.	1	III 39
Bowel	1	III 37
Bronchus	1	IV 29
Cardio/respiratory	8	II 6 III 18 III 29 III 32 III 33 IV 7 IV 11 V 18
Neuro/psychiatric	3	III 19 IV 22 V 16
GI	2	II 5 IV 32
TB	3	II 8 III 36 IV 50
Renal	1	IV 28
Cause unknown	5	III 2 III 10 III 35 III 47 III 48
		Total 25

childhood leukoplakia (Fig. 3). A further 5 patients were examined between 1974 and 1979 and have been included in this review. In Table 5, the patients have been given both the reference number used in the 1973 publication and also the current pedigree number. Since the original study of this group of 21 patients, 5 have developed oesophageal cancer and 1 has had breast cancer. In the 7 non-tylotic patients examined prior to 1979, all are alive and well (Table 6).

The clinical appearance of the preleukoplakia lesions found in childhood have been described as a grey-white lesion affecting practically the whole buccal mucosa and the histological picture was consistent with acanthosis, spongiosis and parakeratosis of the epithelium. The most striking feature was the presence of many large, clear cells throughout the stratum spinosum. There was also a diffuse pattern of keratohyalin granules [12]. In adults the lesions are described as leukoplakia and may also have associated areas resembling the childhood preleukoplakias. No specific clinical or histological characteristics were found in these lesions apart from the large number of oral lesions in the tylotic patients. Ultrastructure analysis of these lesions revealed the presence of intranuclear electron dense particles and similar particles were found in epithelial cells from an oesophageal carcinoma [19].

Leukoplakia is relatively rare in the general British population, 1% in moderate and non-tobacco users and 8% in heavy smokers [20]. Similar findings have been shown in a Swedish study [21]. In a recent worldwide review of oral leukoplakia, totalling 750 000 patients, the total prevalence rate of this condition was found to be 4% [22]. In the assessment of the tylotic patients, 20 out of 21 tylotic patients were found to have preleukoplakia/leukoplakia lesions and therefore there is likely

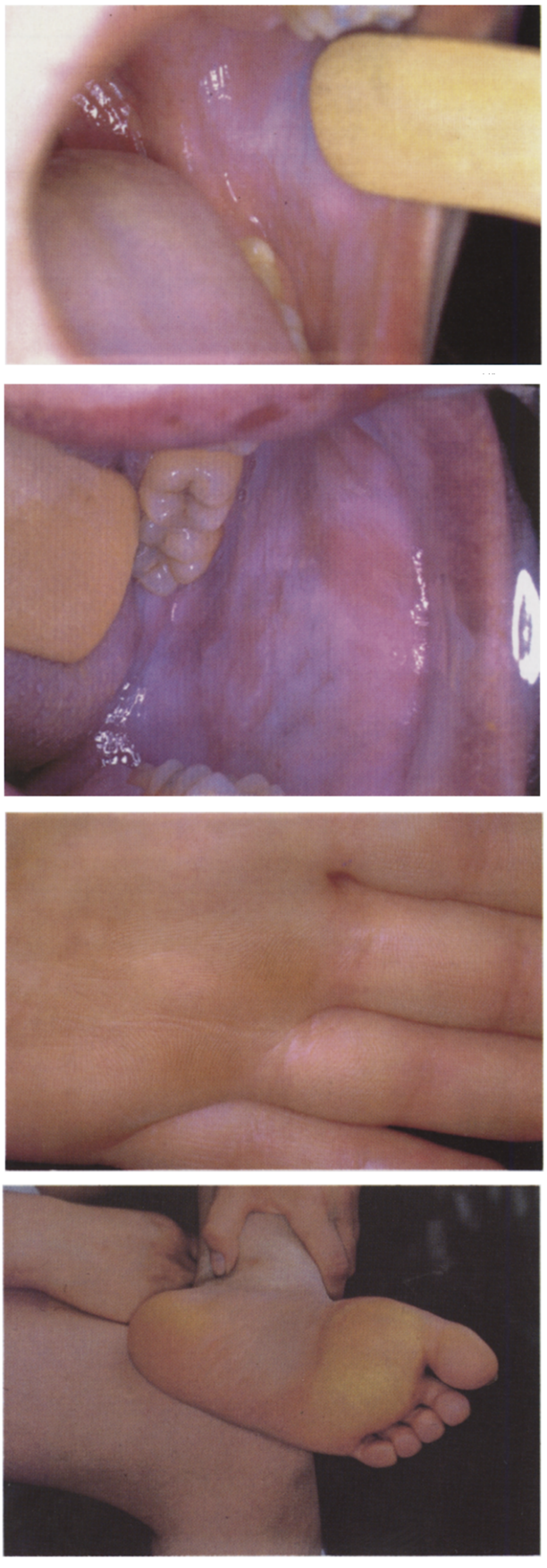

Fig. 3. Clinical appearance of oral lesions in tylotic patients. Pre-leukoplakia in patient V72 aged 12 (a) and leukoplakia in the same patient aged 31 (b). Tylotic hand and feet lesions in the same patient aged 12 (c, d).

to be a definite association between oral lesions, skin lesions and the high probability of developing oesophageal carcinoma.

Associations between lesions of palmoplantar keratoderma and oral lesions in tylotic patients has been described by a number of research groups [7, 9, 23–26]. Fred *et al.* [7] were the first to report this association in a patient who had a combination of palmoplantar keratoderma and lesions of the gingivae and the dorsal surface of the tongue which were described as hyperkeratosis. It is of note that this patient was reported to have had a hard, painless, nonfriable, white gritty substance about 5 mm thick over his gingivae. Five members of a Greek family were found to have focal palmoplantar and severe 'hyperkeratosis' of the oral mucosa in all affected individuals [26]. The age of onset of the hyperkeratosis in these Greek patients was in early childhood or around puberty; a similar age to that reported in the Liverpool tylotic family. However, the associated hyperkeratosis reported by Fred *et al.* [7] and by Laskaris *et al.* [26] is dissimilar to the preleukoplakia/leukoplakia lesions reported by Tyldesly and Osborne-Hughes [12]. The single patient reported by Ritter and Peterson [18] appears to follow the pattern of oral lesions described in the Liverpool tylotic family.

SURVIVAL ANALYSIS OF LIVERPOOL TYLOTIC PATIENTS WITH OESOPHAGEAL CANCER

In several large surveys of oesophageal carcinoma, no familial association is normally found apart from a number of high incidence areas in China, Soviet central Asia and Iran [27–29]. In addition, no significant familial association between tylosis and oesophageal cancer has been found in any of the tylotic families originating outside the Liverpool area. In the tylotic patients reported up to 1958, 95% of these patients would be expected to develop oesophageal cancer by the age of 65, provided that they did not die from other causes [5]. We have re-evaluated all of the six generations and used the Lifetest Procedure to fit survival curves for tylotic individuals in family 'S' [30–32]. It now appears that the probability of developing oesophageal cancer has fallen to 60% by the age of 60 in the tylotic patients. However, there is a 92% chance of dying of oesophageal cancer by the age of 70 in these individuals (Fig. 4). Possible reasons for the reduced probability of developing oesophageal cancer by the age of 65 over the past 35 years may be attributed to the introduction of screening methods or improved treatment after 1957. A number of these patients have been treated with oral retinoids for hyperkeratosis (5–10 years), which have been shown in certain neoplasias to have an anti-cancer effect [33].

CYTOGENETIC STUDIES FOR THE TYLOSIS CANCER GENE

No cytogenetic abnormalities have been found in karyotyped samples of peripheral blood nor from an oesophageal tumour from an affected individual (Owens *et al.*, unpublished). These findings are in agreement with previous cytogenetic investigations on this family [2].

BIOLOGICAL BASIS OF TYLOSIS

The cutaneous lesions of tylosis show marked hyperkeratosis and acanthosis pathologically. The possible changes in differentiation which give rise to these abnormalities could involve any of the proteins, which are expressed during

Table 5. Follow-up of tylotic individuals originally assessed with lesions on the hands/feet and in the oral mucosa

No*	'S' Family No.	Age first seen	Degree of tylosis (feet/hands)	Oral¶ leukoplakia	Pre-leukoplakic	Present age	Fate
1	V 87	4	+	—	+	24	A/W
2	V 79	6	+	—	+	25	A/W*
3	V 73	9	+	—	+	28	A/W
4	V 76	11	+	—	+	30	A/W†
5	V 72	12	++	—	++	31	A/W
6	V 71	13	+	—	+	33	A/W
7	V 74	15	++	—	++		‡
8	IV 74	23	+	—	—	42	A/W
9	IV 73	26	++	+(1)	++	45	A/W
10	IV 39	30	+	+(2)	++	49	A/W
11	IV 20	30	++	+(1)	+	49	A/W
12	V 4	34	++	+(6)	+		D49 CA oeso
13	IV 14	35	++	+(3)	+	54	CA B§ SD‖ A
14	III 54	44	++	+(1)	+		D63 CA oeso
15	IV 10	45	+	—	+		D59 SD‖
16	IV 53	47	+	+(4)	+		D53 CA oeso
26	IV 57	37	++	+(N)	+		D50 CA oeso
27	IV 53	59	++	+(N)	+	72	CA oeso 1956; CA oral 1992; A
28	IV 55	42	++	+(4)	+	55	A/W
29	V 40	14	+	—	+	27	A/W
30	V 38	16	++	—	+	29	A/W

*Non-tylotic †LFU (lost to follow-up) 1985 ‡LFU 1984 §B Breast cancer ‖Senile dementia.
No. = Patient number given in 1973 paper for the oral assessment of the tylotic patients [12].
A number of previously unreported patients are also included in this table [26–30].
¶Number of leukoplakia lesions recorded in parenthesis. N = not recorded; A/W = alive and well; D = dead.
CA oeso. = cancer of the oesophagus; CA oral = oral carcinoma.

Table 6. Follow-up of non-tylotic siblings originally assessed for oral lesions

No.	'S' Family	Age first seen	Oral lesions	Present age	Fate
18	V 88	7	—	26	A/W
19	V 77	10	—	29	A/W
20	V 75	13	—	32	A/W
21	V 104	17	—	36	A/W
31	V 109	4	—	17	A/W
32	V 108	6	—	19	A/W
33	V 39	15	—	34	A/W

No. = Patient number given in 1973 paper on oral lesion in the tylotic patients [12]. A number of previously unreported patients are also included in this table [31–33]. A/W = alive and well.

terminal differentiation of the keratinocyte. These include structural cytoskeletal proteins such as keratins; envelope proteins such as involucrin; membrane glycoproteins and membrane lipids and enzymes involved in corneocyte desquamation. These processes have been little investigated so far in the patients with tylosis, either with or without oesophageal cancer, but some clues are appearing from recent advances in understanding a disorder of keratinisation, bullous ichthyosiform erythroderma, which appears to originate from mutation in suprabasal keratins 1 and 10 [34–36]. Bullous Ichthyosiform Erythroderma (BIE) is an autosomal dominant disease which is characterised by epidermolytic hyperkeratosis pathologically, and clinically by generalised redness and blistering usually present at birth, but marked hyperkeratosis develops later in life and in many kindreds also involves the palms and soles with an appearance very similar to that in tylosis. Keratin mutations have also been found underlying a congenital blistering disease, epidermolysis bullosa simplex, where mutations in the basal keratins 5 and 14 are associated with all forms of epidermolysis bullosa simplex (Weber Cockayne, Dowling Meara and Koebner forms) [37]. Tylosis is also characteristic of Dowling Meara epidermolysis bullosa simplex.

The biology of keratin intermediate filaments has been extensively investigated in the past decade and the analysis of keratin sequences, keratin genes and protein biochemistry of the filaments they form has all led to an understanding of these

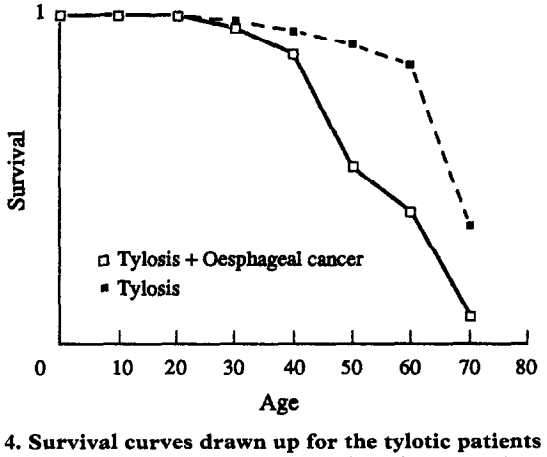

Fig. 4. Survival curves drawn up for the tylotic patients with and without oesophageal cancer based on 1993 data.

major structural proteins of the epidermis. Keratin intermediate filaments assemble into a 10 nm cytoskeletal network forming a dense halo around the nucleus and radiating to interact with the subperiphery and desmosomes [38].

All keratin (+1F) polypeptides have a common structure with an alpha helical coiled core and non-homologous non-coiled carboxy and aminoterminal regions. More than 30 keratins have been identified both in epithelial cells and in hair and nail forming cells (trichocytes) numbered according to gel position. Keratins fall into two groups biochemically, the basic and acidic keratins, which co-express in specific pairs in a cell and tissue specific manner. In the normal epidermis basal cells express keratins 5 and 14 and suprabasal cells express keratins 1 and 10. The basic building block of the intermediate filament is the rod like coiled coil heterodimer comprising one acidic and one basic keratin. These then interact in a complex way to build up the intermediate filament structure. *In vitro* studies introducing mutant intermediate filament genes into cultured cells and into the germ cells of transgenic mice colonies have illustrated that specific regions of the keratin filament are of particular importance in filament assembly. These are helix initiation and terminationa peptides which are highly conserved across the intermediate filament family. Mutations in these highly conserved regions appear to be appearing in the reports of both Bullosa Simplex (EBS) and Bullous Ichthyosiform Erythroderma (BIE) [34, 39, 40]. Keratin mutations in both EBS and BIE are associated with distortion of the filament network to form keratin clumps and bundles and intracellular cytolysis.

POSSIBLE LOCALISATION OF THE TYLOSIS CANCER GENE

Preliminary studies on keratin expression in this family [41], have demonstrated that there has been clumping of suprabasal keratins at both the microscopic and electron microscopic levels and this is highly reminiscent of the changes found in BIE. Therefore it may be argued that a genetic defect in a keratin gene could be the candidate gene in these patients. Sole and palm skin expresses a specific keratin, keratin 9, in suprabasal keratinocytes and this would seem to be a good candidate for possible mutations underlying palmoplantar keratoderma. However, in the tylotic patients of the Liverpool family, the disease is not localised simply to the palms and the soles. The patients have, in addition, mucosal involvement, and subtle follicular changes with follicular hyperkeratosis. The sites that are affected in this family, therefore, are characterised by the expression of keratin 6, 16 and 17, and these are also possible candidate genes to be studied in tylosis.

Many important disease genes have been localised within the past year using a number of approaches. Positional cloning has been used to construct detailed physical maps around closely linked markers as in Kallmann's syndrome [42, 43], fragile X syndromes [44] and colorectal cancer [45]. Another common approach is the use of candidate genes to study genetic inherited diseases, e.g. early onset familial Alzheimer's disease [46, 47], Marfan's syndrome [48], and autosomal dominant retinitis pigmentosa (ADRP) [49, 50]. Genetic studies of the ADRP families provides an example of the very successful use of restrictive fragment length polymorphisms (RFLP) and micro-satellite probes in linkage analysis [49, 51, 52].

Keratin gene chromosome localisation has been established and keratin genes are clustered on chromosomes 12 and 17, therefore, studies are in progress to investigate the linkage of tylosis with the chromosomal locations. There are obviously possibilities that an associated 'tylotic cancer gene' may co-segregate with affected keratin genes. Alternatively the changes in both hyperproliferation and differentiation in the tylotic mucosa may predispose in some way to later malignant transformation. Both of these mechanisms require further investigation. The results of such analysis would provide vital information for those involved in genetic counselling for members of the tylotic family.

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