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Psoriasis : concomitance with atopic dermatitis, age of onset and genetics

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PSORIASIS:

CONCOMITANCE WITH ATOPIC DERMATITIS,

AGE OF ONSET AND GENETICS

by

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SUMMARY

The initial aim of this work was to investigate whether the two dermatological conditions, psoriasis and atopic dermatitis (AD), can co-exist in an individual, either concurrently or consecutively over time, in contrast to the widely believed and taught idea that the two are mutually exclusive. A study was initiated and the relevant details of 428 psoriasis patients, 224 atopic dermatitis patients, and 286 control patients were recorded. The main result of finding 45 patients with both conditions was supported by the family history of both psoriasis and atopic conditions in the families of the probands. A hypothesis for the concomitance is presented.

Questions arose from the initial study on the possibility of two types of psoriasis existing, one of early onset and the other of late onset. Ages of onset were formally analysed by the method of maximum likelihood and showed the presence of two distributions, both normal, divided at the age of 40 years. Two negative binomial distributions were found in the number of affected relatives associated with the age of onset in the probands, divided at the age of 40 years. These results raised questions on the nature of the inheritance of the two onset groups in psoriasis.

Segregation analysis was applied to both early and late onset groups as well as overall. A single dominant or recessive gene model was found to be inconsistent with the data in all groupings. However, a double recessive model indicating the presence of two gene loci, fitted the data for late onset. A multifactorial model of inheritance was a good fit to all the data. Heritabilities and the associated genetic correlations were calculated by the methods of Falconer (1965). These indicated that early onset has a polygenic mode of inheritance mainly due to additive gene effects, while late onset has a more complex multifactorial inheritance pattern with environmental factors and non-additive gene effects playing an important role. Psoriasis patients who have 1 parent with psoriasis have early onset, which also appears to be associated with the HLA-B locus.

It is suggested that any reporting of simple modes of inheritance in psoriasis are specific to certain families or populations, where the multifactorial model of inheritance allows for the possibility of certain genes becoming predominant.

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My husband Professor P.H.S. Smith, supported me financially and also supported me in many other ways and it is to him that I dedicate this thesis.

Every increment of knowledge
comes with its own retinue of complexities.

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LIST OF ABBREVIATIONS AND SYMBOLS

A	allelomorphic gene
A_c	Number of affected relatives (controls)
A_r	number of affected relatives (psoriasis)
a	recessive gene
aabb	double recessive gene
AD	atopic dermatitis
Aff.	affected
B	-Chapter 4- Both (Psoriasis + AD)
B	-Chapter 5- allelomorphic gene
b	recessive gene
b_{AP}	regression of additive genetic variance on phenotypic variance
Both	Psoriasis + AD
C.I.	confidence interval
Cont	controls
d.f.	degrees of freedom
disp.	dispersion
DZ	dizygotic (as in twins, where one or more genetic factors are different)
f	frequency
G	Gwynedd
h	square root of heritability
h^2	heritability
HLA	human leukocyte antigen
K	Kent
M	mean (MLP plot)
m^2	homozygous (double recessive model)
m^2,2mn,n^2	genotypic frequencies in the zygote (double recessive model)
2mn	heterozygous (double recessive model)
MLP	Maximum Likelihood Programme
MZ	monozygotic (as in twins, identical genotypes)
n	number
n^2	no affected allele involved (double recessive model)
N_c	total number of relatives (controls)

N_r total number of relatives (psoriasis)

No. number

OR odds ratio

P proportion

p probability (statistical)

p^2,2pq,q^2 genotype frequencies for a population in Hardy Weinberg Equilibrium

p,q,r,s gene frequencies

Par. parents

pr frequency of double recessive gene in the parents

prop. proportion

Ps psoriasis

Q_1 lower quartile

Q_2 upper quartile

q% percentage of affected relatives

r coefficient of relationship between relatives

r_G genetic correlation

RR relative risk

S standard deviation (in MLP)

S^2 variance

S.D. standard deviation

$s.d._G$ genetic standard deviations

S.E. standard error

section 3.3.1 An example of reference to a section in Chapter 3

sibs siblings

sqrt square root

V_A additive genetic variance

V_D dominance variance

V_E environmental variance

V_{EP} epistasis interaction variance

V_G genetic variance

V_{NA} non additive genetic variance

V_P phenotypic variance

x	mean liability in units of phenotypic standard deviations (unless specified otherwise)
x/h	mean liability in units of genetic standard deviations
Z/z	height of the ordinate of a normal distribution in standard deviation units
β	Greek symbol used in mathematical formulae
γ	" " " " " "
θ	" " " " " "
μ	mean
σ	standard deviation
σ^2	variance
χ^2	chi square
Σ	summation of the quantity following sign
$<$	less than
$>$	greater than
$\leq$	less than or equal to
$\geq$	greater than or equal to

CHAPTER 1

INTRODUCTION AND BACKGROUND TO RESEARCH

1.1 Introduction - Definitions, Literature Review and Objectives of the Study

1.1.1 What is Psoriasis?

Psoriasis is a chronic dermatosis which is present in roughly 2% of a Caucasian population, such as that of Great Britain, in both males and females, but may show world-wide variance in different races and climates (Braathen et al, 1989; Lomholt, 1963; Watson, 1984). It can occur at any age but is predominantly post-pubertal in onset.

Psoriasis is an inflammatory and hyperproliferative, but benign, disorder of the epidermis in which there is increased cell production. This gives rise to immature cells with an abnormal keratin layer forming, which then flakes off in excessive quantities. Its aetiology is not fully understood but it is known to be generally of a hereditary origin, with "triggering" factors required, such as stress (Seville, 1977) or Streptococcal infections (Norrlind 1950), to promote the condition from a latent or non-clinical state into a clinical expression of the disease. It can affect the whole body and its prognosis is that, once initiated, it is usually of a chronic or recurring nature, but can become quiescent. The typical lesion is a well demarcated and raised patch with whitish scales, which on removal reveal tiny bleeding points known as Ausptiz's sign.

Psoriasis is socially disabling with patients suffering the embarrassment of being covered with unsightly vivid red plaques and shedding skin scales which can be seen, for example, on clothing and furnishings.

1.1.2. What is Atopic Dermatitis?

Atopic dermatitis (AD) is the principal skin manifestation of the atopic diathesis, an increased liability to form reagin antibodies in response to stimuli. Other important atopic conditions are asthma and hay fever. Not all atopic patients develop atopic dermatitis and this means that although about 30% of a Caucasian population are potential atopics (Visscher et al, 1989), AD is present in about 2-10% of this type of population, in both males and females (Hanifin, 1984). The incidence for atopy is reported to be increasing (Taylor et al, 1984) especially asthma in children, but there is inconsistency in reporting of prevalences. It is unclear as to whether there is a real increase or just that there is more awareness and better methods of reporting. These authors were of the opinion that there may be changing environmental issues promoting the expression of the atopic diathesis.

AD is predominantly a disease of infancy and usually resolves itself in childhood, although it is possible that a "flare-up" can occur at any age. Genetic factors are important to the predisposition of the individual, but environmental factors play a large part in the phenotypic expression of atopic dermatitis. The typical lesion is red and scaly with lichenification and this is sometimes exudative. The particularly intense pruritus which accompanies this makes the patient scratch in response and this leads to further lichenification and infections can be introduced as a result. (Rajka, 1986) Internal factors, for example, stress and hormonal factors (Kemmet, 1989), and external factors, such as house dust mites, animal hair and chemicals, can exacerbate the condition (Rajka, 1983).

Atopic dermatitis patients suffer the physical discomfort of an intolerable itch which can disturb sleep patterns and be quite disabling. Their reactivity to many stimuli often dictates which type of employment they can tolerate.

1.1.3 Diagnostic Difficulties with Atypical Cases

These two inflammatory conditions, psoriasis and AD, both common disorders in the general Caucasian population, are clinically distinct in their typical forms and diagnosis is easy, according to clinically standard criteria. Atypical forms, however, can cause some confusion of diagnosis and both in their very mildest forms may be overlooked in the presence of the other condition (Gardener and McKay, 1989; Archer, 1986).

1.2 **Origin of initial study**

Dr W.E. Beer (W.E.B.), a consultant dermatologist at Ysbyty Gwynedd, Bangor, the District General Hospital for Gwynedd, North Wales, noted, in the course of his clinical experience of over two decades, that a high frequency of psoriasis patients had atopic dermatitis and similarly that atopic dermatitis patients had a high frequency of psoriasis. Also, psoriasis patients gave a frequent personal or family history of the other atopic manifestations.

This was at odds with clinical teaching and widely accepted belief that psoriasis and atopic dermatitis rarely occur together in the same individual. Some researchers have claimed that, in fact, the two diseases are mutually exclusive (Christophers and Henseler, 1987) and that opposing pathomechanisms may be responsible for this.

No prospective study to date had been specifically designed and carried out to test whether this belief held under a rigorously controlled examination of the prevalence of psoriasis in atopic dermatitis patients and vice-versa. The increased reporting of pathomechanisms, which W.E.B. noted had features common to both conditions, prompted the need for epidemiological research to back these laboratory findings.

1.3 **Psoriasis - literature review**

1.3.1 Early Historical Identification of Psoriasis

Early historical identification of psoriasis perplexed clinicians and researchers. Reports on the nomenclature and the exact forms of the disease reflected its enigmatic nature; for example, as early as 400 BC, Hippocrates probably encountered psoriasis under his heading of "lopoi" (to scale), but later reports, such as that of Celcus, 25 BC - 45 AD, did not recognise it as a separate disease, but grouped it along with impetigo. He did, however, give a recognisable description of psoriasis in "De re Medica". Introduction of the word psoriasis was attributed to Galen, 133-200 AD, who used the Greek form of the verb "to itch", but his accompanying description of the disease is more like that of seborrhoeic eczema as he describes blepharitis and scrotal rash (Holubar, 1990).

Early confusion with leprosy persisted and those afflicted with psoriasis often suffered the same fate. Even Willan (1798) did not distinguish between the two diseases and perpetuated the misunderstanding, but is credited with the first detailed clinical description of psoriasis. The final and definitive division of leprosy from psoriasis was due to Hebra (1859).

1.3.2 Development of the Subject

Elliot (1889) thought he understood psoriasis when he described it as "not only amenable to treatment, but curable" in the first volume of the British Journal of Dermatology. Thomas Bateman (1817) wrote about Willan's description of psoriasis and subdivided it into types; guttate, plaque, palmar and chronic with thick scales. In the French edition of Kaposi's textbook (Kaposi, 1891), a very specific psoriasis pointer was introduced when it was reported that Auspitz had described the bleeding points when scales are removed. In this same book, Köbner was reported as describing an observation that in some people psoriasis broke out at a site of trauma, and he

concluded that "a peculiar disposition is located in the skin of psoriatic patients that remains latent for years at a time, but produces this chronic form of inflammation of the skin under the influence of a great many internal and local stimuli". This showed a basic understanding of the nature of psoriasis. Radcliffe Crocker (1903) published a general book on diseases of the skin in which there was a detailed description of the subdivisions of psoriasis and the likely spread. He also reported that most patients first develop the disease before the age of 30 years, 22% between 30 years and 50 years, and 5.5% over the age of 50 years.

1.3.3 Epidemiology

Early on, there was little reporting of diseases associated with psoriasis, but Bourdillon (1889) described the features of psoriatic arthritis, which are now accepted.

Farber and Nall (1982), in "Epidemiology in Psoriasis Research", stated that there was a dearth of information on the course of psoriasis, with the exception of earlier research by Lomholt (1963) and Hellgren (1967), and no large studies have been done since then. They suggested that Government support of population studies would help. This was echoed by Christophers (1986) who pleaded for more studies on the epidemiology and emphasised that there is not enough data on younger psoriatic patients. Significantly, he stated "There could be diseases showing certain pathophysiological aspects in common with psoriasis and this would be of help in answering some basic questions such as: are epidermal skin diseases more frequently associated with psoriasis?"

Lindegard (1989) investigated disease association with psoriasis in his study on hospitalised patients in Gothenburg, Sweden, over a nine year period. Prominent amongst these associations were viral infections, alcoholism, hypertension, pneumonia, liver cirrhosis, urticaria and rheumatoid arthritis, which were all highly significant ($p<0.001$). Also, of relevance to this study,

asthma in females was significantly associated with psoriasis. They recognised that there had been reports, in the past, of an increased incidence of asthma and hay fever associated with psoriasis, but claimed that they were not conclusive because of the lack of controls involved. Because of the nature of the study group, only the more severe cases of psoriasis were recorded and the examination was done by several doctors. Only concurrent incidences of psoriasis and other diseases were noted. They emphasised the need for further studies of disease association in order to complement the pathophysiological work being done elsewhere.

In the study by Kavli et al (1985) lifestyles were examined and they found that an intake of fruit and vegetables was negatively associated (a protective factor) with psoriasis and an intake of coffee positively associated (a risk factor), at $p<0.05$. They quoted Voorhees (1983), who had postulated that coffee altered physiological pathways. They also noted an increased prevalence of smoking in psoriasis patients.

Braathen et al (1989) also found an increased prevalence of smokers among psoriasis patients (58.2%) compared with controls (43.5%). Furthermore, they recorded a significant positive correlation ($p<0.01$) of alcohol consumption and psoriasis. They concluded that there was possibly under reporting of alcohol consumption and quoted Midanik (1982) whose study indicated the possibility of up to 50% underestimation of alcohol consumption by patients themselves.

1.3.4 Prevalence in the Population

Lomholt (1963), in a study of psoriasis in the Faroe Islands, found 2.84% with psoriasis out of a population of 10,984. It could be argued that his findings may be influenced by inbreeding in an enclosed community, as can happen elsewhere with other diseases. His prevalence was higher than that reported by Hellgren (1967) on a large random population sample in three regions of Sweden: generally he found that the prevalence was higher in

colder areas, ranging from 1.2% to 2.6% , when all grades of severity of psoriasis were included.

Brandrup and Green (1981) studied 3892 individuals in Denmark. They found a prevalence of psoriasis in 4.2% of men and 3.3% of women, but this was adjusted for false positives after a report from the Danish Twin Register (Brandrup et al, 1978) had revealed an estimated 24% of false positives, using similar methodology. They did not include any person under 16 years of age.

Farber and Nall (1982) carried out a postal questionnaire of several countries in order to gain more widespread knowledge of the disease. In particular they noted whether there were any differences between the sexes in different races and discovered that the sex ratios were approximately equal, apart from Kuwait, where there were 10% more males than females. Specific cultural reasons were suspected in this reporting.

Kavli et al (1985) estimated psoriasis prevalence in Norway from people who came forward as volunteers in a survey for coronary risk factors. They reported a much higher prevalence of psoriasis than former studies, claiming it was 4.8% in men and 4.9% in women. These figures raise questions about the possibility of a bias in the volunteers. The most recent study by Braathen et al (1989) on psoriasis in Norway demonstrated an overall 1.4% prevalence with no differences between the sexes. At the same latitude, Lindegard's (1989) study of hospitalised patients indicated an incidence of psoriasis of 0.23%, which does not represent an estimated population prevalence.

Direct comparisons between these results are not possible because of varying methodological approaches towards collecting the data and analysing it.

1.3.5. Age of Onset

Kononen et al (1985) studied all (1863) members of the Psoriasis Society of Helsinki. They found that the mean age of onset was 25.5. years, but two-thirds of patients showed signs of the disease before the age of 30 years. Farber and Peterson (1961) and Hellgren (1967) both showed that psoriasis can manifest itself at any age and last for any length of time, with an unpredictable course. They stated their belief that psoriasis occurs infrequently below the age of 3 years, with a peak just after puberty.

Farber and Nall (1982) found that the mean age of onset varied between 23 years (Denmark and Kuwait) and 36 years (Hong Kong). The authors speculated that , since Hong Kong patients had a later age of onset, they would exhibit a higher threshold (lower risk) for psoriasis and stated that this would probably fit with a particular genetic mechanism.

Henseler and Christophers (1985) examined the notes of 2147 hospitalised patients and found two distinct ages of onset in psoriasis. Their early onset group had peaks at 16 years for females and 22 years for males, while the late onset group had peaks at 60 years for females and 57 years for males. A fuller search of the literature for studies on age of onset is included in Chapter 4.

1.3.6 Aetiological Factors

The triggering factors which evoke a manifestation of the disease are subject to widely differing reporting of this by the patient and also different interpretation by the physicians. Farber and Peterson (1961) concluded that psoriasis was an expression of a disturbed environment around the patient and the reaction to that environment.

Lomholt (1963) stated that, for the course of the disease, the younger the age of onset the stronger the impact of the environmental factors. These were in the main; injury to the epidermis by trauma, that is the Köbner phenomenon (Kaposi, 1891), injury by chemicals or systemically administered

drugs. The Köbner factor had been investigated by several researchers including Stankler (1969) after previous reports (Farber et al, 1965) had suggested that the depth of damage was important in the inducement of psoriasis in susceptible individuals. This showed that epidermal damage was necessary, as dermal damage alone was insufficient.

1.3.6.1 Immunological response

Streptococcal infections had been implicated by Norlind (1950) and it became recognised that this was a particularly frequent trigger. The mechanism of this is still under debate, but a possible explanation comes from Swerlick et al (1986) who noted a cross reactivity between Streptococcal antigens and keratinocyte components.

The immunological response to Streptococcal infections also fits in with the statistical decision theory that Morris (1987) applied to psoriasis age of onset data (Farber and Nall, 1974). This indicated that the increasing chance of error in the immune system with age will be offset by a reduced incidence of first contact with the bacteria, plotted as a function of age in the patient. This theoretical curve closely fitted Farber and Nall's data of age of onset in 5,600 psoriasis patients.

Further emphasis for this comes from McFadden (1990) who put forward a hypothesis that psoriasis may be subjected to natural selection processes. He stated that a prevalence of psoriasis may be likened to what has happened to certain genes as a direct response to an environmental hazard, such as a common infection. The particular infection which he suggested as having a similar interplay to psoriasis, is scarlet fever (a streptococcal infection which involves some immunological pathomechanisms in common with psoriasis). He postulated that this should be reflected in the global distribution and found such a link - the temperate climates once had endemic scarlet fever and now have a much higher prevalence of psoriasis than other climatic regions. In conclusion, he suggested that psoriasis is "an evolutionary response to the

natural check of scarlet fever as a disease related to streptococcal hypersensitivity".

1.3.6.2 Stress

Emotional factors (stress) are often implicated in the onset of psoriasis by the patient, but this may be enhanced in retrospect as shown by Farber et al (1965), and so it was thought that as well as being a trigger, it may well be partly symptomatic.

As in many other conditions, stress has been shown to precede the onset of psoriasis. Seville (1977) examined 132 psoriasis patients who had been cleared of the disease by the use of topical Dithranol and followed them up for 3 years. Of these 51 (39%) claimed to have a clinical onset of the disease after a stressful event that had happened in the previous month. Surprisingly, they found that the prognosis is better when psoriasis was triggered by a stressful event possibly because it is transient in its effect.

Another research group have found that stress occurred during the year prior to the onset of psoriasis in 70% of patients. They used an indicator of severity of stress, called the "Paykel Scale of Stressful Events" (Polenghi, 1985). The importance of psychological insight as a good prognostic feature was emphasised by Payne et al (1985) in a study of 32 patients.

1.3.6.3 Drugs

Incidents of drug aggravation of psoriasis have been reported. The most frequently implicated drugs appear to be beta-blockers, anti-malarial drugs and anti-inflammatory drugs. Fry (1988) suggested that this may be a patient-specific response, as certainly not all psoriasis patients taking the drugs are affected. He concluded that their role in the biochemical pathways is too complex to be understood at present.

1.3.6.4 Genetics

Braun-Falco (1967) stated that he thought that the predisposition to psoriasis is inherited and that therefore the abnormalities ought to affect the whole skin rather than just affected areas.

Variances in occurrence of psoriasis in different ethnic groups support a common ancestry theory. In American-Indians the disease is rare (Kerdal-Vegas, 1974), also in West Africans, although common in East Africans (Lomholt, 1971). American blacks with West African ancestral roots also appear to have no psoriasis in the population (Kinney, 1971).

Some early studies of families suggested that psoriasis inheritance may be explained by an autosomal dominant single gene, for example Romanus (1945), Hoede (1957), Ward and Stephens (1961), Abele et al (1963) and Kimberling and Dobson (1973). Others found evidence for a double recessive mode of inheritance (Steinberg, 1951).

However, in the majority of studies on the genetics of psoriasis, a hypothesis of multifactorial inheritance has been found to explain the data, for example (Watson et al (1972) Ananthakrishnan et al (1973) Ananthakrishnan et al (1974).

Twin pair studies have been carried out, and were hoped to be a powerful tool for delineating the genetic contribution. For example, Brandrup et al (1978), Farber and Nall (1974) indicated that a multifactorial model best explained their data.

During the 1970's techniques for detecting human leucocyte histocompatibility antigens (HLA) were being developed. Histocompatibility antigens are inheritable but whilst they themselves are not directly responsible for the disease, the close association that is shown to exist, means that the HLA status gives a good indication of the risk of the disease (Fry, 1988).
Williams (1976) stated that he thought HLA associations would give a good

indication of the likelihood of developing psoriasis when eventually identified. Subsequently many studies have examined the HLA associations in psoriasis.

"It is now thought that a simple monogenetic type of inheritance has been excluded in psoriasis" (Fry, 1988). To avoid repetition of all the literature review on the genetics of psoriasis, a full review is contained in Chapter 5, where the genetics of psoriasis will be developed.

1.3.7. Pathophysiology

Many pathomechanisms are involved in psoriasis and an extensive literature review has been undertaken by W.E.B. in relation to those in common with atopic dermatitis (Beer et al, 1991). This is reported in the Appendix, merely for completion, as a full understanding of these is considered to be outside the scope of this thesis.

1.4 **Atopic dermatitis (AD) - literature review**

1.4.1 Early Historical Identification of Atopic Dermatitis

The term "atopy" comes from the Greek word "atopia" which means strange disease. A Frenchman, Besnier (1882), first described the eczema which he called eczema diasthetique. It is called prurigo Besnier in many parts of Europe today. Brocq (1902) used the term diffuse neurodermatitis, suggesting that the disorder was caused by a nervous condition. The introduction of the word "atopy" is attributed to Coca and Cooke (1923) who applied it to a group of diseases, including asthma and hay fever, which occurred in individuals who had a family history of susceptibility to reactions to reagins. This term was adopted generally and Wise and Sulzberger (1933) in America introduced the term "atopic dermatitis" to describe the principal skin manifestation of atopic disease.

1.4.2 Development of Atopic diathesis and AD

One of the earliest recognisable mentions of the atopic diathesis occurred when Blackley (1873) became aware of his own allergy syndrome in the form of hay fever. He proceeded to experiment upon himself by testing his own reaction to pollen.

At the beginning of the twentieth century Ramirez first showed the antigen effect by giving blood from a person who was sensitive to horse dander, to a "normal" recipient, who then developed asthma on subsequent exposure to horses. When tested, both donor and recipient then reacted positively to horse dander antigen. This idea was later developed by Prausnitz and Kustner (1921) who experimented on themselves. Prausnitz was the recipient of serum from Kustner, who was sensitive to fish. The site of the intradermal injection was later exposed to fish antigen, which produced a strong reaction. It was this test, mainly, which enabled the properties of antibodies to be examined. Coca and Grove (1925) found reagin antibodies in atopic patients and demonstrated that these could be transferred to others using the Prausnitz-Kustner (P.K.) reaction. An interest in histamine response in AD patients was started by Williams (1938) who described an exaggerated reddening of the skin of atopic dermatitis patients when injected with histamine intramuscularly. This was followed up by Katz (1941) who showed an involvement of histamine as a mediator of anaphylaxis in tests on blood.

Understanding of the epidemiological aspects of AD was increased when Clarke (1928) reported that although atopy could be transmitted to offspring in a different form, it tended to be transmitted in the same form of the disease. Later, Rostenberg and Sulzberger (1937) described a reduced incidence of contact dermatitis in AD patients. Around this time Feinberg (1939) described seasonal exacerbation of AD and the phenomenon of white dermographism was described by Whitfield (1938) who stated that he thought

it to be a marker for AD, since he estimated that 70% of these patients demonstrated this.

The controversy over the naming of the skin disease associated with atopy continued. Rajka (1968) suggested using the term atopic "dermatitis" which he believed covers all morphological events and is more descriptive of the condition than the word eczema. Ackerman and Ragaz (1984) agreed with this and called for "eczema" to be removed from the dermatological terminology. Rajka had his own definition which included the compromise "eczematous":- "Atopic dermatitis is a specific dermatitis in the abnormally reacting skin of the atopic resulting in itch with sequelae as well as eczematous inflammation". AD, however named, became accepted as another "atopic" condition, like asthma and hay fever (Brereton et al, 1959; Rajka, 1960). Champion and Parish (1968) were of the opinion that AD could be found in individuals who showed no demonstrable allergic or anaphylactic reaction, such as food allergies, contact allergies and insect bite allergies. The term "eczema" can be used often to describe the skin manifestations of anaphylaxis and, in contrast to AD, anaphylactic reactions can occur in individuals who had no family disposition to this. To distinguish between atopy and anaphylaxis, they proposed the term "atopic dermatitis" as it best described the sense of there being a skin condition associated with atopy. It was agreed that terminology was less important than developing a uniform definition of the disease.

Geha (1986) stated that although AD is widely accepted as a multifactorial disorder, studies have been done on one aspect at a time, often displaying the lack of objectivity of the researcher, who naturally has a specific background and skills, and who pursues his own particular line of interest. He also stated that "investigators of eczema have approached the problem from their own biases. As an immunologist, my own bias is that the disease results from a central disturbance in the immune system". Graham-Brown (1988) opined that "there is no doubt that some aspects of the management of

AD have suffered from the almost fanatical zeal with which enthusiasts have sold their ideas".

1.4.3 Epidemiology

Few epidemiological studies had been done on AD, the emphasis being on laboratory work. Rajka (1983) examined the disease associations that had been reported in the literature - these included autosomal dominant ichthyosis, geographic tongue, cataracts, Wiskcott Aldrich syndrome and Job's syndrome.

An allergy study (Dupont, 1988) showed that allergies were less important for patients with AD than for those with asthma and hay fever. House dust mite, already established as a factor in asthma, has also been implicated in AD (Norris et al, 1989). They used skin patch testing to show this. Mites and pollen were thought by Young et al (1989) to be primary culprits for the seasonal exacerbation found to be a feature of AD. Estimation of asthma and hay fever in the AD patient have been so well documented in the past that these manifestations of the atopic trait are not currently being investigated for their presence in AD. Nickel sensitivity has been said to be common in AD (Marghescu, 1985) and is considered to be a possible diagnostic feature of AD, although other contact allergies are not.

1.4.4 Prevalence in Population

Rajka (1960, 1961, 1975) carried out a six year study of all aspects of AD on patients in Stockholm. He reported that the course of the disease was unpredictable and gave results of his literature search of other authors studies with regard to prevalence. He stated that it was "clearly very difficult to evaluate uniformly these data which are so very different from the point of view of the material collected". He also highlighted the importance of not assuming that all cases of infantile eczema were classified as AD - a mistake which Walker and Warin (1956) stated had been made by other authors.

These authors found that 3.1% of children in Bristol, England, had the condition. Hanifin (1984) reviewed the literature and found reports varying from 0.7% over all ages to 4.3% of children under the age of 5 years in the U.S.A.

Different approaches to collection of the data can influence the results, but race, climate and age of cohorts also play a role. Most studies take a prevalence in a population at one instant in time, rather than a lifetime's occurrence of the condition. A few recent studies have been carried out. Rajka (1986) and Saurat (1987) estimated the prevalence of AD to be about 5% of the population, especially in people of the Caucasian race who are thought to be more prone to AD. Some specific studies have looked at children, and of these, the prevalences reported vary widely: Schachner et al (1983) found that the prevalence in childhood had risen considerably since the second World War, from 5.1% to 12.2% . This, they suggested, was possibly due to factors such as changes in feeding patterns, secular attitudes to reporting (admitting) the condition, altered medical diagnosis and environmental factors. A rise in the general prevalence of AD was also reported by Schultz-Larsen et al (1986) who found that between 1960 and 1974 the prevalence in Denmark had increased from 3% to 10% of the population and stated that, in their opinion, this represented a true increase rather than changes in reporting. They thought that the increase was probably due to changing environmental factors.

1.4.5 Age of Onset

AD is observed to occur at any age, but a typical age of onset is thought to be between 2 and 6 months. Occasionally it has been detected in babies younger than this and also has been observed to start in people over the age of 50 years (Champion and Parish, 1968).

1.4.6 Aetiological Factors

It has been noted frequently that AD patients' skin itches more readily than normal skin. Rajka (1968) showed this and suggested that it is best to think of these patients as having an inherently itchy skin. Increased cutaneous infections have also been reported, especially of Staphylococci bacteria (Rajka,1963). Hanifin and Rogge (1977) discussed this as it seemed to them that there was a cause and effect argument here as to whether the mere act of itching and the resultant trauma damaged the skin and allowed infection to set in. One of the consequences of itching was shown to be lichenification (damage to the epidermis causing thickening and deep lines to form). Some considered this to be a primary feature of AD (Hanifin and Lobitz, 1977), but others thought it was not peculiar to the atopic individual (Champion and Parish, 1968).

Keratosis pilaris and ichthyosis have been shown to be common in atopic patients (Wells and Kerr, 1966). This dryness of the skin was demonstrated to lower resistance to irritants and alkaline substances. Vascular abnormalities were described by Rajka (1975); vasoconstriction of the small blood vessels occurred, resulting in the appearance of blue fingers on exposure to cold. It was unclear as to whether white dermographism was due to small vessel constriction or to oedema as other forms of dermatitis also demonstrated this reaction (Uehara and Ofuji, 1967). Rajka (1983) stated that he believed that important steps have been made in the understanding of the interrelations between immunobiochemical advances and the vascular response of the inherently dry skin of AD. This gives rise to the itch and skin alterations which are characteristic of the condition.

Schultz-Larsen et al (1986) stated that "Our knowledge of the aetiology of AD may still be considered fragmentary". They also stated their opinion that many studies are selective and biased, and that difficulties in the definition of AD do not help this.

1.4.6.1 Immunological response

The identification of immunoglobulin E (IgE) as a reaginic antibody by Johanssen (1968) confirmed the presence of a reaginic mechanism operating in AD. High levels of IgE were shown to be responsible for the anaphylactic hypersensitivity in patients. It was recognised that a high IgE level was not specific to AD and was present in many conditions, although it could be helpful in substantiating a diagnosis (Nye et al, 1975). Hanifin (1980) found that histamine is raised in tissues, but high plasma levels have only been found in the most severe cases.

Streptococcal pyoderma may complicate AD, but the most important infections are due to Staphylococcus aureus and herpes simplex virus (HSV). Aly (1980) found that 90% of AD patients were colonised with Staphylococcus aureus, concentrated mostly over the uninvolved skin areas. A significant increase in HSV infections were prevalent, as well as upper respiratory tract infections. He suggested that this was due to immune dysfunction rather than the skin dysfunction of AD itself.

1.4.6.2 Stress

Flare-ups of AD with emotional stress have been demonstrated. Saurat (1986) carried out an objective test on student volunteers which indicated that AD, in common with some other skin conditions, was subject to psychological stress. A study by Kemmett (1989) also indicated a premenstrual flare of AD, but whether this was due to psychological stress or endocrinological factors is unclear.

1.4.6.3 Drugs / food allergies

Drugs have not seriously been implicated by anyone in the recent literature in the aetiology of AD. Food allergies are still a controversial area. Some dermatologists consider that diet plays no real part in the condition,

others report on specific reactions that have exacerbated AD. Egg albumin especially seems suspect to some. Langeland (1982) found that egg allergy is associated with high IgE levels and also with the more severe forms of AD. A study by Sampson (1983) showed that a method for testing for food allergy (RAST) was as unreliable as prick tests in its diagnoses. The high IgE levels found in AD patients give rise to false positive results if used as diagnostic criteria.

While it is not disputed that some people react adversely to foods, it is not clear as to how many people actually experience worsening of the AD itself. Currently, the thinking is that since evidence is so scant, diet does not play an important role in the consideration of AD (Task Force in Paediatric Dermatology, 1986). Graham-Brown (1988) agreed with this and showed particular concern about inappropriate manipulation of children's diets.

1.4.6.4 Genetics

Rajka (1975) estimated from his own studies and a review of the literature that 60% - 70% of AD patients have a first degree relative with one or more atopic conditions, that is, either the skin manifestation AD, or asthma, or hay fever, compared with an incidence of 30% in a non-atopic control group. He had earlier carried out studies on twins (Rajka, 1960) when pairs of both monozygotic (MZ) and dizygotic (DZ) twins revealed a higher concordance rate than other relatives, supporting the hypothesis of genetic predisposition. It was suggested that the atopic diathesis was the inheritable factor rather than any one particular manifestation (AD, atopy, or hay fever). Also, the age of onset and the clearance of each condition, as well as the affected sites in AD, could be transmitted (Schynder, 1960). This concept was adopted generally.

That most patient with AD have a family history of "atopy" is well established and that AD is primarily a hereditary disease is not in doubt. However, there is a lack of precise familial information on the condition.One study, however, has been carried out: Schultz-Larsen et al (1986) specifically

studied twin pairs in an attempt to assess the importance of the genetic influence. They sent out a postal questionnaire to all twins on a register who were born in a period of 14 years and who lived in one complete geographical area, a region in Sweden. All the cohorts were examined subsequently by a dermatologist and a full history recorded. They were each defined as MZ or DZ by serological testing. They found that if one MZ twin had AD, the other had a far higher risk (86%) of developing the disease than in DZ twins or ordinary siblings (21% for both groups). This shows that an individual's genotype is vital to the risk of developing this condition. The reporting of less than 100% concordance, however, was thought to be probably due to other multifactorial factors. Graham-Brown (1988) has called for further work on the genetics of AD generally, and specifically on the HLA system.

1.4.7 Pathophysiology

An evaluation of common pathomechanisms in psoriasis and AD are given in the Appendix to this chapter and in Beer et al (1991).

1.5 **Aims and objectives of the initial study**

One of the aims of the initial study was to demonstrate whether psoriasis and AD occurred in the same individual or not. Another aim was to respond to the call for more epidemiological studies on disease association with psoriasis (Christophers, 1986). The main objectives were:-

(a) To investigate the clinical relationship between psoriasis and AD in patients and in their first degree relatives by rigorous clinical examination and structured clinical questionnaire.

(b) To assess the prevalence of atopy , that is asthma and hay fever, in the patients and in their first degree relatives.

(c) In the course of the clinical examination, to observe the presence of other diseases, for example, seborrhoeic eczema and nummular eczema, and to examine clinical criteria useful in differential diagnosis in clinically unclear cases.

(d) To undertake a general literature search on psoriasis and AD to elucidate any factors common to both and for background understanding.

(e) To determine whether there is an association between psoriasis and AD and environmental factors such as lifestyle and diet. (This is to be analysed as a separate major study and is not included in the thesis.)

1.6 **Research arising from initial study**

The exact age of onset was not considered to be critical to the study of concomitance between psoriasis and AD, however, later it was decided to examine the age of onset of psoriasis in greater detail. Christophers (1986) had emphasised that he considered the age of onset in psoriasis to be an important factor when considering psoriasis patients.

The exact age of onset of psoriasis patients in the present study were included where possible on the proforma. On examining in detail the data in respect of age of onset, it was discovered that there was a distinct pattern in onset of psoriasis, indicating two age of onset peaks at approximately 20 years of age and 55 years of age, with a minimum at around 40 years. To see if this could be substantiated, it was decided to collect a second set of data retrospectively from patients notes in two hospitals in Kent, England, where careful note had been taken of the age of onset of psoriasis patients. These two sets of data were then formally analysed. Results of this led to questions

on the nature of the inheritance of psoriasis and the possible genetic models involved.

1.7 Aims and objectives of the study on age of onset in psoriasis and the application of genetic models

This study aimed to investigate the age of onset distribution in psoriasis patients to see if any obvious pattern arose. Secondary to this, another aim was to see if there was any association between this distribution and the numbers of relatives who were reported as having psoriasis, to discern any correlation between them. It was hoped to look at the genetic patterns involved between first degree relatives for inheritance patterns.

The main objectives were:-

(a) To apply mathematical modelling to the ages of onset of psoriasis patients and assess the distributional properties.

(b) To assess the distribution of the number of affected relatives for various ages of onset of the psoriasis patients.

(c) To investigate the distribution of patients' ages at the time of examination and relate this to their ages of onset.

(d) To use segregation analysis between the groups to elucidate if the data approximated to any of the standard genetic inheritance models of dominance and recessivity.

(e) To demonstrate whether or not the data fitted multifactorial inheritance models.

(f) To calculate the "heritabilities" of different onset groups, by using an appropriate model, and also the "heritabilities" for different types of first degree relatives.

(g) To demonstrate whether or not any changes in "heritabilities" were due to increased or decreased genetic liability or due to environmental variances.

1.8 **A brief outline of the thesis**

CHAPTER 2 describes the design of the initial study on the concomitance between psoriasis and AD. It sets out the initiation of the research and the collection of the database from dermatology clinics in Gwynedd. A questionnaire (Appendix A) had been designed to record all information from psoriasis patients, AD patients and any patients found to have both these conditions, plus control patients. This information included personal data, age of onset of the condition, personal and family history of relevant conditions, plus diet and lifestyle factors. Also, the topographical skin features presenting in the patients on a thorough clinical examination.

The definitions used to delineate features and conditions are listed and a literature search to help identify these are included in Appendix B.

CHAPTER 3 presents the results of the concomitance of psoriasis and AD study and the discussion of these results. Demographic details of each patient group are tabled and an age profile of the patients given. The main result of the numbers of patients found in the study to have both psoriasis plus AD are presented with supporting results from the incidence of psoriasis and atopy in the families of these patients. Clinical details of all 45 patients with dual pathology are tabled with additional information thought by the dermatologist to be of interest.

A hypothesis is presented to try to explain the finding of the apparent increased prevalence of the two conditions. The findings of other researchers in relation to the presence of dual pathology are discussed.

The remainder of the chapter deals with the dermatological features on clinical examination. These are tabulated and compared for those which are significantly different between patient groups. This gives rise to criteria which can be used as "markers" for psoriasis or "markers" for AD and comments are made on the position of the group with dual pathology with respect to these features.

CHAPTER 4 is an expansion of aspects arising out of the initial study, where the ages of onset of psoriasis were realised to be of interest, since a suggestion had been made in the literature that there may be two types of psoriasis, partially based on age of onset. These onsets of psoriasis patients in this study are analysed in 5 year intervals. Two peaks of onset result and a preliminary analysis demonstrates the possibility of the presence of a mixture of two distributions. A further sample was collected, retrospectively, from patients notes in clinics in Kent, to substantiate this. Formal analysis, by means of the method of maximum likelihood, is applied to both sets of data, both separately and combined.

The numbers of relatives affected by psoriasis, of the Gwynedd patients, in association with the age of onset categories, is tabled. This tabling, which presents percentages of affected relatives in each age of onset to age in the patient at the time of examination, automatically corrects for the increasing number of relatives the patients would accumulate with increasing age. The mean percentages of affected relatives is then analysed and the resulting histograms and maximum likelihood plots are presented.

CHAPTER 5 analyses further the nature of the familial association of the two onset groups in psoriasis found in Chapter 4 and applies possible genetic models. To this end a new file was created containing data on all relatives individually, which is not available on the main data file but present on the proforma. Segregation analysis of the relationship between relatives is carried out. A fit of both autosomal dominant and autosomal recessive single gene models to the data is tried, before a double recessive gene model is applied. The results lead to the application of a polygenic or multifactorial model. A Minitab computer programme was written to facilitate repeated calculations of complex formulae of "heritabilities" with their standard errors. These heritabilities are an estimate as the data did not contain the age of onset, or the age, of the relatives. A comparison is made with other studies and conclusions debated.

CHAPTER 6 is a summary of the findings of Chapters 3 to 5 and additional comments. Conclusions are drawn and implications pointed out. Suggestions for further use of the database and other future related research are made.

APPENDIX

Dr. W.E. Beer's literature search on pathomechanisms associated with both psoriasis and atopic dermatitis.

Scientific investigation into the pathology of the psoriatic lesion was greatly promoted by studies in cell kinetics (Van Scott and Ekel, 1963). In more recent times attention has turned to the elucidation of the underlying pathology to explain keratinocyte proliferation (Valdimarsson et al, 1986). Meanwhile the study of atopic dermatitis lingered on the role of reagins, mast cells and the environment. In the last two decades the emphasis in research into both conditions has been channelled into the immunological consequences of possible aberrations of cyclic nucleotide function and mediators of inflammation. A number of common pathomechanisms have come to light. This, in itself, is not surprising because both are inflammatory conditions and one might expect therefore to find similarities.

Both disorders are said to have a defective cyclic nucleotide metabolism (Voorhees, 1982; Archer, 1987). Associated with this defect are other features such as βeta adrenergic hyporesponsiveness (Archer et al, 1987; Yoshikawa et al, 1975) and a raised phosphodiesterase in mononuclear cells in both conditions. This had, at first, been thought to be a marker for atopic dermatitis (Archer et al, 1988; Holden et al, 1986). Protein kinases, at the effector end of cyclic nucleotide metabolism, show a deficiency of c-AMP-dependent protein kinases (PKA) in fibroblasts and red blood cells in psoriasis (Raynaud et al, 1989). In atopic dermatitis, histamine desensitization is responsible for a reduced response of PKA and PKC activity to histamine (Trask et al, 1985). There is an interplay of agonists, enzymes, cytokines and mediators of inflammation. It has not been easy to determine whether some of the cellular control mechanisms are secondary to the influence of circulating inflammatory mediators or to a primary enzyme defect (Coulson et al, 1991).

A major advance in the investigation of these two diseases took place when it was shown that cell mediated immunity played an important role in their pathogenesis (Holden, 1990; Butler, 1984). This led to a study of T cell subsets. It has been reported that there is a deficiency of total T cells and T4 cells in both conditions and that there is a deficiency and defective function of suppressor cells in atopic dermatitis. In psoriasis, T8 numbers are normal but there is the possibility of a deficient antigen specific suppressor cell function (Guilhou and Clot, 1984; Grove et al, 1985; Baker et al, 1984; Braathen, 1985; Sauder et al, 1980). However, some of these observations have been disputed (Holden, 1990; Rola-Pleszczynski and Blanchard, 1981). A reduced autologous mixed lymphocyte reaction (auto MLR) is associated with skin inflammation. It is an immunological response by T cells to surface antigens on non T cells, such as β lymphocytes, macrophages and dendritic cells, and it is altered in diseases considered to be mediated by the immune system. If there is a decrease in disease activity there is an increase in the auto-MLR. It is reduced in atopic dermatitis and more so in psoriasis, where it tends to be low even in remission, thus indicating that it is not just secondary to inflammation (Zachary and MacDonald, 1983; Sowden et al, 1990; Terui et al, 1990). Helper cells play a predominant role in both psoriasis and atopic dermatitis (Leung et al, 1983). Interleukin II receptor levels are raised in the sera of psoriasis and atopic dermatitis; an indication of T cell activation and proliferation (Rasanen et al, 1987; Kapp et al, 1988). The role of cellular immunity is well illustrated by the clearance of severe psoriasis in one patient after an allogenic bone marrow transplantation (Editorial, 1989) and also both by the transfer of latent atopy by bone marrow transplantation and clearance in another case (Kapp et al, 1988; Eedy et al, 1990).

A defect in delayed hypersensitivity reactions resulting in a decreased response to allergen and mitogen has been reported in both psoriasis and atopic dermatitis (Gardembas-Pain et al, 1990; Saarinen 1984). This has, however, been questioned (Agost, 1988). IgE is elevated in 80% of atopic dermatitis patients and in 46% of those with psoriasis (Epstein and Maibach, 1965; Moss

et al, 1982). CD23/FceRIeRII, the low affinity Fc receptors for IgE and its multiple soluble breakdown products (SCD23) may have a possible role in IgE regulation. Expression of CD23 was found to be significantly elevated on mononuclear cells and small adherent cells in both psoriasis and atopic dermatitis (Müller et al, unpublished). No significant increase in SCD23 levels was detected. (It is believed that cell bound CD23 is a non specific marker of inflammation).

Mediators of inflammation have been compared. Leukotreines have a chemotactic role in both psoriasis and atopic dermatitis (Voorhees, 1983; Ruzicka et al, 1984). Complement activation and circulating complexes have been studied. The levels of certain fractions in the complexes in both psoriasis and atopic dermatitis, such as IgG, C_3 and IgE are significantly elevated (Kapp et al, 1986; Kapp et al, 1985). Platelet activating factor, a chemotactic, vasoactive, and phospholipase C activator, plays a role in both conditions (Tagami et al, 1987; Michel et al, 1988). As might be expected, plasminogen activators help clear fibrin deposition (Grondahl-Hansen et al, 1985; Lotti et al, 1989).

Mast cells are noted in early guttate and relapsing psoriatic lesions and they are increased in the dermis in atopic dermatitis (Schubert and Christophers, 1985; Mitchell et al, 1986). Eosinophilic activity is indicated by the presence of eosinophilic granular protein . In atopic dermatitis it is seen with mononuclear cells in the elastic tissues of the upper dermis and in psoriasis it is found with granulocytes in the upper dermis and stratum corneum (Lundin et al, 1990; Leiferman et al, 1985).

Trace element studies have shown raised copper and decreased selenium in the blood, plasma and lymphocytes of both conditions. Elevated levels are also seen in seborrhoeic dermatitis. Selenium is an essential component of the enzyme glutathione peroxidase (GSH-Px) which has a role in preventing free radicals and lipid peroxidase from accumulating. These elements have a potential to damage cell membranes (Hinks et al, 1987; Michaelsson et al, 1989).

CHAPTER 2

DESIGN OF THE STUDY
(Materials and methods)

2.1 Introduction

This chapter describes the initiation of the study and the personnel involved. The design of the study is also laid out, that is the sample size required, ethical considerations, design of the questionnaire with the definitions of the questions and features to be noted. Appendix A gives the full questionnaire used. Appendix B gives a review of the literature which was required in the design of the section of the questionnaire concerned with the clinical features of the patient.

2.1.1 Setting up the Study

To achieve the aims and objectives of the research, a collaborative study was set up between the Department of Dermatology of Gwynedd Health Authority and the Centre for Applied Statistics, University of Wales, Bangor.

The personnel involved were Dr. W.E. Beer (W.E.B.) a consultant dermatologist at Ysbyty Gwynedd, who initiated the study; Dr C.M.E. Rowland Payne (C.M.E.R.P.) a consultant dermatologist at Kent and Canterbury Hospital, who expressed an interest in the main aims of the study and was particularly interested in the clinical criteria involved (he also contributed extra data for use in Chapter 4); Dr. P.H.S. Smith, Medical Physicist, who was originally asked to give advice on using a scientific approach and who suggested a collaborative work involving a professional statistician; Dr. J.Y.Kassab, Director of the Centre for Applied Statistics agreed to help the dermatologists design the questionnaire and added some specific questions related to the epidemiology and genetics of psoriasis and AD. The author was employed initially as a research assistant to interview the patients and collect the data in the

dermatology clinics and later, as a student, carried out the literature review, statistical analysis of the data and interpretation of the results under the supervision of Dr. Kassab.

2.2 **Sample size**

Sample size determination was complicated as this was not a straightforward clinical trial with expected response rates. No clinically significant value could be attached as happens, for example, in drug trials. The estimation of sample size needed to detect differences of clinical importance was set on the conventional basis of having a power of 80% (1-β), where β is the probability of making a Type II error, which is the probability of accepting the null hypothesis of no difference between groups where in fact a difference exists. The significance level was set at a conventional 5%. This gives $Z_\alpha = 1.65$ and $Z_\beta = 0.84$, where Z is the upper critical value of the normal distribution.

It was assumed that the likely main outcome of this study would be a comparison of the number of psoriasis patients one would expect to have atopic dermatitis and vice-versa. Although the proportions of these in the Gwynedd general population are unknown, reported prevalences (see Chapter 1) from other populations could give a guidance to this.

On the basis of the prevalence of psoriasis being 2% in the population and atopic dermatitis being 5% - 10%, the sample size in each group is given by:-

$$n = (Z_\alpha + Z_\beta)^2 \{ p_1(1-p_1) + p_2(1-p_2) \} / \delta^2$$

(Kassab, 1988).

where p_1 = proportion of psoriasis patients in population

and p_2 = " " atopic dermatitis " " "

and $\delta = p_2 - p_1$

By substitution:- n = 460, where p_2 is taken as 0.05

and n = 68, where p_2 is taken as 0.10

Because of the multiple comparisons that were to be made between the groups and the rate of referrals to the clinic, a figure of 300 for each of the three groups was thought suitable and this could be collected within a reasonable time period of 18 months or so, the length of time allocated to the study. As the study progressed, it became evident that our proportions of patients were not equal (mainly a function of referral) and so the original 900 had to be increased to 1,200 in order to get sufficient numbers of atopic dermatitis patients. The proportions half-way through the study were psoriasis 0.45, atopic dermatitis 0.22, and controls 0.33. The final numbers were 428 psoriasis, 224 atopic dermatitis, 286 controls and the 45 patients who had both conditions.

2.3 **Origin of patient data**

All patients routinely referred to the out-patient dermatology clinics in Gwynedd between April 1988 and July 1990 were clinically examined by W.E.B. for the presence of psoriasis or atopic dermatitis or both conditions.

The controls were required to be patients free from psoriasis or atopic dermatitis or other inflammatory conditions. There was a need for the clinician to eliminate confusion of the clinical manifestations and minor features of any other inflammatory skin disease which might mask or compete with the features of psoriasis and AD. Hence the final decision that the controls had, therefore, to be those individuals who presented with non-inflammatory lesions. These were mostly seborrhoeic warts and naevi, but also conditions like basal cell epitheliomata and Bowen's disease.

The control patients were used to examine the significance of the differences in the occurrence of asthma and hay fever in the patients. Also,

they were used to investigate the significance of the differences between all the groups in the occurrence of these conditions in the first degree relatives.

All patients, after being clinically examined and the clinical data recorded by W.E.B., were immediately interviewed by the author for relevant details of personal history, family history, diet and lifestyle factors. The results were recorded on the same proforma (Appendix A) as the clinical data.

The population of Gwynedd is relatively static and this means that some of the patients, and their families, had been seen by the same dermatologist (W.E.B.) for 25 years, and thus many familial details could be confirmed. The details of only first degree relatives were included in the study.

2.4 **Ethical considerations**

The main aims and objectives of the research work were submitted to, and approved by, the Ethical Committee of Gwynedd Health Authority. The patient's consent was formally sought before the interview took place by asking the patient to read a short note, in English or Welsh, on the study. They were given assurances of confidentiality of the information, whilst it was emphasised that failure to take part would not compromise their treatment. No patient objected to being examined, or refused to co-operate.

2.5 **Patient details required**

2.5.1 The Main Priorities of the Examination

One of the main aims of the study was to examine the prevalence of atopic dermatitis in psoriasis patients and vice-versa, along with collecting other evidence to substantiate or confirm the basic findings.

The study also set out to investigate the patients' personal data, their dermatological medical history, their family's medical history, their lifestyle and diet as well as to carry out a thorough clinical dermatological examination.

The clinical criteria used in searching for any evidence of either disorder were a result of the combination of an extensive literature search (Appendix B) and the judgement of the relevant criteria by the two dermatologists involved (W.E.B and C.M.E.R.P.).

W.E.B., in his clinical examination, took notes of the apparent surface features as they presented on the patient, ticking off a list of features that were "clinical criteria", in a systematic way. The patient then fitted into the diagnostic categories of (1) psoriasis (2) atopic dermatitis (3) control (4) psoriasis plus atopic dermatitis. This examination was always carried out by the same clinician (W.E.B), to ensure consistency in the examination and thus subjective factors arising from differing diagnostic approaches between clinicians were avoided.

The rest of the interview was completed solely by the author, for the same reasons as above. This was carried out after the clinician had finalised his section and decided on the diagnostic category of the patient. The medical notes of the patient were available throughout for checking of details, such as past medical history and onset of the condition.

2.5.2 The Questionnaire Proforma

The questionnaire proforma was designed by Dr. J.Y. Kassab, using information from the clinicians. Epidemiological and family history questions were added as it was thought that these might produce information on the aetiology and modes of inheritance of the two main conditions (Appendix A).

The questionnaire recorded the patients' personal details, including age and age of onset of the condition (onset was not relevant to controls). It also recorded their personal history of psoriasis, atopic dermatitis and other atopic conditions and the presence of these in their immediate family members (first degree relatives). The latter were divided into parents, siblings and children, but not divided by sex. Clinical features presenting at the time of examination

were noted methodically and the patient questioned about other clinical history which was noted if it was at all relevant to the study.

2.6 Typical features used in categorising patients

Psoriasis was defined as being sharply demarcated, erythematosquamous lesions which may be of any size and either solitary or more extensive. They have a characteristic redness, usually covered in silvery scales (except when in the flexures), with typical sites being the trunk, scalp and limbs, while the face is not usually affected. Nail pitting and discolouration is characteristic and interphalangeal joints may be affected (Beer et al, 1992). Supportive of the diagnosis is a family history of the disease and an initiation or exacerbation of the condition following Streptococcal throat infection or reaction to certain drugs implicated in promoting psoriasis, such as beta-blockers. Those AD patients with palmoplantar pustulosis were not included as there is still controversy as to whether this is part of the psoriatic diathesis, or whether it is a separate entity (Gardner and McKay, 1989).

Atopic dermatitis (AD) was defined as a pruritic disorder presenting with a fluctuating but chronic course. It is predominantly a disease of childhood where eczematous lesions of the head and neck are prominent during infancy and then the flexures become involved. Older children and adults feature lichenification due to the trauma of sustained scratching. A family history of atopy and a raised serum IgE determination can help in identification (Beer et al, 1992).

Histological identification was not done as others found this unhelpful (Schmidt, 1990). Some psoriasis patients had lichenified patches but these were defined as psoriasis only unless there was further evidence of AD. Some atopic dermatitis patients who had "psoriasisform" lesions were classified as AD only, unless they had conclusive signs of psoriasis. This means that the

psoriasis plus AD group included only those with unequivocal signs of both diseases.

The research of others was borne in mind when identification criteria were applied and these published markers for both psoriasis and atopic dermatitis are further discussed in Appendix B. Also included in this appendix is seborrhoeic eczema as sometimes delineation between this and psoriasis or atopic dermatitis is difficult and there is a dispute, especially in infants, of its diagnostic criteria.

2.6.1 Definitions in the Patient's History

In the section on the patient's history in the questionnaire (Appendix A), the following definitions and conditions were used.

Asthma - prepubertal onset asthma, not that which occurs later in life which can have a large psychological element.

Hay fever - only truly seasonal rhinitis, and not perennial rhinitis. (Being part of the atopic diathesis, these two conditions helped confirm a diagnosis of atopic dermatitis).

Migraine - headaches which are one sided or preceded by an aura, not simply bad headaches for whatever reason.

Papular urticaria - discrete excoriated papules notably on the distal aspects of the limbs.

Intolerance to wool or animal hair - self explanatory, it often helped in identifying atopy and is considered by some to be a primary feature of atopy (Appendix B).

Itching - separated into 4 groups:- (0) No itching. (1) Itching on the rash only. (2) Whole skin itching. (3) Severe generalised itching, and especially at night. Psoriasis patients mostly fall into the first two groups, whereas atopic dermatitis patients experience the whole skin itch or severe generalised itching and therefore fall into the second two groups.

Seasonal changes - whether the patients experienced a pattern of worsening or alleviation of his condition during the year. Generally, psoriasis patients experience an alleviation of their condition in the sun, whilst atopic dermatitis patients may also benefit from the sun, but low humidity may often make their condition worse.

2.6.2 Definitions in the Clinical Examination

The clinical examination (Appendix A) resulted in the following conditions being recorded according to the agreed definitions:-

Seborrhoeic dermatitis is an erythematous, scaly eruption with onset after puberty, at two or more of the following sites: scalp/hairline; eyebrows; nasolabial folds; periauricular; and presternal. (See also Appendix B)

Dandruff - flaking from scalp.

Hyperhidrosis - rivulets of axillary sweating or a"spangled" glistening of the palms.

Retro-infra auricular intertrigo - erythema, ulceration or fissuring, especially behind and under the ear lobe.

Scaling within the ear - scaling especially in the external auditory meatus.

Xeroderma - dry skin to the touch.

Keratosis pilaris - keratotic follicular papules on the outer aspects of the limbs.

Periorbital shadowing - shadows, under the eyes.

Fine hair - unmanageable, hair diffracts light when illuminated from behind.

Lichenification - thickening of the skin with accentuation of the skin markings. It is often on flexural or extensor surfaces of limbs.

Nummular eczema - round discs of eczema, usually in older patients.

Dennie Morgan folds - two or more creases on the infraorbital skin.

Hyperlinear palms - increased numbers of palmar lines with marked accentuation.

Acrocyanosis - blue tinge to the skin of the fingertips.

Many of these have been reported as being primary or secondary features of psoriasis or atopic dermatitis and are discussed in Appendix B.

2.6.3 Equivocal Diagnosis and Information

Because of the difficulty of making diagnosis from an obscure skin rash, or other feature, on the patient's first visit, some patients' questionnaires were held back for review of their clinical situation. Sometimes laboratory evidence, for example, IgE level estimation, was needed to eliminate other possible causes for the skin disturbance and often the condition had manifest itself more clearly on subsequent clinic visits. These questionnaires were then included in the survey when a definite diagnosis had been made. Those patients who had poor recall were eliminated, unless the information could be obtained from the patients' notes or other reliable sources.

2.7 **Statistical analysis**

The questionnaires were coded and input to the Vax 8650 mainframe computer at the Centre for Applied Statistics, University of Wales, Bangor. The statistical packages SPSS and Minitab were used to analyse the data.

The statistical analysis included calculations of basic statistics (percentages, means, standard deviations, frequencies, etc.), tests of significance of relationships between groups and more complex analyses, including maximum likelihood estimation and genetic modelling of inheritance.

APPENDIX A

THE QUESTIONNAIRE

Notes

(1) Originally, the age of onset of the patient's condition was categorised as - 1. (0-9) 2. (10-19) 3. (20-49) 4. (50+) years, as this was thought sufficient by the dermatologist at the time. Later it was decided to record the actual age of onset of patients for more formal analyses of this variable. Actual age of onset was then recorded, either by questioning the patient or from the patient's notes, where possible.

(2) Serum immunoglobulin (IgE) level estimation was halted after 279 patients had been done, since insufficient funding was available for large numbers of these, also it was not thought to be of critical help to the diagnosis. Total eosinophil count was halted for the same reasons.

GWYNEDD HEALTH AUTHORITY/U.C.N.W.

PSORIASIS AND ATOPY STUDY, 1988

CONFIDENTIAL

(Fill in boxes, circle or tick as appropriate)

1. Study number

2. Hospital number

3. Name

4. Address

5. Age

6. Information from Parent/Guardian Yes/No

7. Sex Male/Female

8. Occupation

9. Date seen

10. Diagnosis group Psoriasis/Atopic eczema/Control

11. Age of onset(years)

Patients	Present		Past	
	Yes	No	Yes	No
12. Psoriasis				
13. Atopic eczema				
14. Asthma				
15. Hay fever				
16. Migraine				
17. Papular urticaria(reaction to insect bites)				
18. Intolerance to wool/animal(dogs, cats etc)hair				
19. Combination skin				
20. Seasonal changes				
21. Others(specify)				

21. (a) Itching? 0

1

2

1&2

Family History

State the number in each category

	Parent		Sibling		Children		Total	
	Yes	No	Yes	No	Yes	No	Yes	No
22. Psoriasis								
23. Flexural eczema								
24. Asthma								
25. Hay fever								
26. Migraine								
27. Papular urticaria(reaction to insect bites)								
28. Intolerance to wool/animal(dogs, cats etc)hair								
29. Others(specify)								

Examination

30. Psoriasis Yes/No
31. Atopic eczema. Yes/No
32. Seborrhoiec dermatitis Yes/No
33. Nummular eczema Yes/No
34. Fine hair Yes/No
35. Dandruff Yes/No
36. Retro/Infra auricular interigo Yes/No
37. Scaling within ears Yes/No
38. Periorbital shadowing Yes/No
39. Dennie Morgan folds Yes/No
40. Xeroderma Yes/No
41. Keratosis pilaris Yes/No
42. Hyperlinear palms Yes/No
43. Acrocyanosis Yes/No
44. Hyperhidrosis Yes/No
45. Lichenification Yes/No
46. Others(specify) Yes/No

Laboratory Investigation

47. Full blood count
48. IgE
49. Total eosinophil count

Possible Coexisting Diseases

50. Liver cirrhosis — Yes/No
51. Lung cancer — Yes/No

Life Style and Diet

52. Number of cigarettes smoked per day
53. Consumption of alcohol(units per day)
54. Consumption of coffee and tea, cups per day — < 1 / 1-4 / 5-9 / 10-

Intake of Food:

daily=1/ 2 or 3 times a week=2/ once a week=3/ < twice a month=4

55. Fresh fruit and vegetables — 1 / 2 / 3 / 4
56. Fish as a main dish — 1 / 2 / 3 / 4
57. Turkey or chicken as main dish — 1 / 2 / 3 / 4
58. Red meat(beef,mince,lamb,pork)as main dish — 1 / 2 / 3 / 4
59. Stress. — Yes/No

APPENDIX B

Review of the Literature for Diagnostic Criteria

Diagnostic criteria used in dermatology to help identify dermatological conditions are still in dispute. Psoriasis is fairly easily defined, but some of the features which are alleged to identify an atopic dermatitis patient particularly causes controversy amongst researchers. Seborrhoeic dermatitis is also included, because of a similarity of features with both these conditions.

Since there are no laboratory markers which uniquely identify these conditions, it was decided to summarise the leading papers in this field and include features in the questionnaire which were considered to be relevant.

1. Clinical features of atopic dermatitis

The classical criteria for making the diagnosis of atopic dermatitis is that proposed in an paper by Hanifin and Rajka (1980). This criteria has been adopted and quoted as such frequently in the literature by researchers. However, many others have questioned their approach. The identification of minor features that help in a diagnosis is subject to the individual dermatologist's attitudes and experience. The following is a summary of the relevant papers.

Hanifin and Rajka (1980) carried their extensive work on the identification of atopic dermatitis when the diagnosis is unclear in an attempt to create an objective measure of the likelihood of the presenting condition being atopic dermatitis. They suggest a requirement of 3 BASIC features plus 3 or more MINOR features for a firm diagnosis.

BASIC

Pruritus

Lichenification

History of atopy, either (a) personal or (b) in the family

MINOR

Xeroderma

Hyperlinear palms

Keratosis pilaris

Skin test reactions

Early age of onset

Skin infections

Hand and foot dermatitis

Nipple eczema

Cheilitis

Recurrent conjunctivitis

Dennie Morgan folds

Elevated serum IgE

Subscapular cataracts

Periorbital darkening

Facial pallor

Pityriasis alba

Anterior neck folds

Itch when sweating

Intolerance to wool

Perifollicular accentuation

Food intolerance

Emotional factors

White dermographism

Svensson et al (1985) derived a point system for significance of features. Patients with more than 15 points were considered to meet the criteria for atopy.

1 point for $p < 0.05$

2 points for $p < 0.01$

3 points for $p < 0.001$

This basically means a combination of value 15 or over, when compared with controls. This was a complex study, and not readily comparable with other studies because of the different scoring system. The patients had been chosen because they probably had atopic dermatitis, based on flexural itching and lichenified eczema. They found the same basic features as Hanifin and Rajka, with the addition of seasonal variation, xerosis, tension factors (stress), IgE >80ku/l and irritation from textiles ($p < 0.001$). All the minor features they found were included in the list of Hanifin and Rajka, except for nummular eczema ($p < 0.01$) and pompholyx ($p < 0.05$).

Kang and Tian (1987) also evaluated the clinical and laboratory findings of atopic dermatitis, in the light of the continuing controversy, and bearing in mind the criteria of Hanifin and Rajka. For diagnosis of "atopy" they suggest a minimum of 2 of their BASIC features or 1 BASIC plus 2 MINOR ones. The basic features identified were mostly the same as those in Hanifin and Rajka's list, with additional minor ones included.

However, they found that some of the minor features suggested by others were often difficult to discern, or did not contribute to the diagnosis in any way. These were:-

DIFFICULT TO DISCERN	**NOT SIGNIFICANT**
Anterior neck folds	Migraine
Itching	Pompholyx
Wool intolerance	Geographical tongue
Environmental/emotional factors	Dennie Morgan folds
IgE results	Dust mite allergy

Deipgen et al (1989) constructed a score system, based on values which they thought might help in making a firm diagnosis of atopic dermatitis. They identified their atopic dermatitis patients using the Hanifin and Rajka method and then looked at them further to identify other features.

Patients with more than 10 points were considered to be atopic, 6-10 points made them possibly atopic. Their significant MINOR features were itch when sweating, intolerance to wool, xerosis, white dermographism (3 points); AD of scalp in newborn, cheilitis, hyperlinear palms, pityriasis alba (2 points); family history of atopy, hay fever, asthma, conjunctivitis, hyperhidrosis, Dennie Morgan folds, nickel sensitivity, food intolerance, facial erythema, photosensitivity, keratosis pilaris (1 point).

Hyperlinear palms was considered by Mevorah et al (1985) to be not significant and suggested that these findings were more of a marker for autosomal dominant ichthyosis. The suggestion had been made earlier by Uehara et al (1981) that hyperlinear palms were a sign of ichthyosis in an atopic dermatitis patient. They found that 37% of these patients had ichthyosis in the winter season.

In contrast to this, Fartasch et al (1989) suggested that hyperlinear palms was a phenotypic marker for atopic dermatitis. They carried out histological examinations on all their patients and identified true autosomal dominant ichthyosis. They found lower concomitance of the two diseases than studies done without the histology (4% as compared with 30-40%).

Mevorah et al (1988) carried out an evaluation of Hanifin and Rajka's criteria, but assessed only 7 of the original features, plus one of their own - infra auricular fissuring, which they found to be a significant feature.

An American study by Visscher et al (1989) recruited cohorts through an advertisement for people with "skin problems" to volunteer for research. This would inevitably have influenced their controls against which they measured the features of atopic dermatitis patients for validity of atopic criteria. Their identification for selection of an atopic dermatitis patient, compared to

a "control", included some of the features they were measuring. These were pruritus, family/personal history of atopy, hand dermatitis, cheilitis and nipple eczema. Their findings of features that are specific to atopic dermatitis as opposed to other (unidentified) skin problems were similar to Hanifin and Rajka's, but they found that Dennie Morgan folds and ichthyosis were not necessarily features of atopic dermatitis. The objectives of this study were difficult to define, especially in view of the biased controls. They found that most of each of their groups complained of "dry skin" and said it was probably due to the harsh climate of Denver, Colorada.

Rowland Payne C.M.E. (1988), in a personal communication gave his impressions on the best features to be taken into account when assessing a patient. He presented, in descending order of importance, the MINOR features he found to be most helpful, in his experience:-

Helpful	**..and to a lesser extent..**
Fine hair	Viral warts
Intolerance to wool	Xeroderma
Hyperlinear palms	Dennie Morgan folds
Keratosis pilaris	
Periorbital shadowing	

The situation may be summarised by Graham-Brown (1988) who stated that, in a classical case of atopic dermatitis there is no difficulty with the diagnosis, but "there are many patients who do not fit into the neat box ..... if research into therapy and pathogenesis is to be meaningful, we must have some means of establishing that we are talking about the same disorder."

This problem has not been fully resolved yet and an agreed laboratory marker remains elusive. Archer (1986) suggested that we have currently to settle for good clinical criteria in identification of atopic dermatitis and that "Hanifin and Rajka" give the best criteria, with a few debatable modifications.

2. Clinical features of psoriasis

The various forms that psoriasis takes do not lead to as much confusion as atopic dermatitis in the identification of the condition - psoriasis is usually unmistakeable, except in a very mild form. Hellgren (1967) gave features that were definitive of psoriasis, in his opinion, in his classic work on psoriasis:-

either 1 of **Auspitz sign**, tiny bleeding points on removal of scales.

Histological picture, typically of parakeratosis, acanthosis, oedema, microabscesses (Munro), extended rete ridges, clubbing of the papillae, and thinning of the stratum Malpighi.

Arthritis of the rheumatoid type.

Nail changes - punctate nails.

or 3 of **Typical onset** of psoriasis.

Heredity.

Traces of healed lesions on typical sites.

Previous diagnosis of psoriasis.

Response to therapy for psoriasis.

Menter and Barker (1991) thought that there are 3 BASIC features of the typical lesions of psoriasis, of any type:-

Erythema - characteristically vivid red.

Scaling - silvery and with Auspitz sign developing on removal of last layer.

Thickening - in varying degrees, sometimes depends on the site.

Also indicative of psoriasis are the well demarcated appearance of lesions and typical sites involved. Nail pitting and discolouration as well as arthritic involvement are common manifestations. A background of a family history of psoriasis and a personal history of napkin psoriasis or cradle cap helps diagnosis. Onset often occurs after a Streptococcal throat infection and as a response to certain drugs, for example, antimalarials, beta blockers, lithium and anti-inflammatory drugs.

3. Clinical features of seborrhoeic eczema

Bastuji-Garin et al (1988) described the results of a Parisian study on patients admitted to a casualty department. They gave a list of features that were found to be present in patients who had been identified as having or had seborrhoeic dermatitis, that is, those susceptible to it, and compared these with controls. The most commonly occurring features were, in descending order:- dandruff, combination skin, scaly ears, acrocyanosis, hyperhidrosis, outer toe web intertrigo, auricular fissuring, nummular seborrhoeides, pompholyx.

The **first five** of these were considered to be the most helpful, and it was thought that **at least 3 of these** could give clear differentiation from controls. However, psoriasis patients were excluded from those examined.

CHAPTER 3

PSORIASIS AND ATOPIC DERMATITIS CONCOMITANCE

3.1 Introduction

This chapter starts with a brief report of the research relating specifically to the concomitance of psoriasis and AD. Basic statistics and demographic details are given in section 3.1.3, and the main results of the study into the concomitance of the two conditions in section 3.1.4. This latter section includes clinical details of the group of patients who were found to have both conditions, either concurrently or consecutively. The family history of either condition is also reported and matching of these to the patient's diagnosis highlighted (section 3.1.5).

These results are discussed in section 3.2, where a hypothesis is presented to explain the prevalence of psoriasis in AD patients and vice-versa. The results and opinions of other researchers, specific to the concomitance of psoriasis and AD, are discussed in relation to these results.

The findings on the concomitance of psoriasis and AD, which form this first part of the study, were published in Beer et al (1992).

Section 3.3 deals with the results of examining the clinical features in the patients which are specific to psoriasis or AD, or those found in the patients with dual pathology. The prevalences of these were initially compared with their prevalences in control patients. A comparison of the clinical features of psoriasis and those of AD is presented, that is, a comparison between two inflammatory conditions in respect of these features which may give a clearer differentiation of the two conditions.

3.1.1 Research Relating to Psoriasis and AD Concomitance

Since psoriasis and AD had been believed to rarely occur together in the same individual, some controversy over the co-existence of the conditions had been reported in the literature. The study of Christophers and Henseler (1987), which stated that the two diseases were mutually exclusive, was the main research paper to have been published when this present study was being carried out. Much of the discussion in the literature has been concurrent with this study and some has arisen from the basic results of it. This literature is included in the discussion of the results (section 3.2.6), because of the interactive nature of the comments. However, other research is relevant to this topic. For example, the prevalence of psoriasis in populations has been reported in section 1.3.4 and that of AD in section 1.4.4. The familial incidences of psoriasis was estimated by Hellgren (1967) in a population study in Sweden. He found that 45.1% of psoriasis patients had a family history of psoriasis, that is, at least one first degree relative with the condition. A similar figure was found by Farber and Nall (1974) in the U.S.A. The familial incidence of AD has been reported by Rajka (1975) as approximately 60-70% of AD patients having a first degree relative with the condition. Other family incidences have been estimated, but are not directly comparable because of the methodology used and classification of "familial incidence". This sometime includes second and third degree family members, and sometimes means the prevalence of the condition in all relatives.

The identification between psoriasis and AD in children and in particular in relation to psoriasiform napkin dermatitis and seborrhoeic dermatitis is still debated. For example, Rasmussen et al (1986) studied 18 patients with psoriasiform napkin dermatitis and discovered on follow up that 2 had developed psoriasis and 2 had developed AD after all "napkin dermatitis" had cleared. Neville and Finn (1975) stated that two types of napkin dermatitis could be identified - psoriasiform and seborrhoeic. In a study of 113 children with napkin dermatitis, the psoriasiform groups tended to get psoriasis later (at

5-13 year review) and in the seborrhoeic group the children tended to get AD later. Conflicting views on this are still held and indicate particular confusion in diagnosis of infants. Lowe (1988) stated that, in childhood, psoriasis of the scalp needed to be separated from childhood AD.

3.1.2 Missing Values in Study

This study contains missing values for the family history of relevant conditions, where the patient either did not have the information or could not recall the details. Of psoriasis (Ps) patients, the complete family history of 413 of the 428 patients, could be ascertained. The figures for AD were 223 out of a total of 224 patients, for controls (C) 283 of the 286 patients, but all of the 45 patients with both psoriasis plus AD (Ps + AD) had their full family history.

Other missing values were those when the patient's age of onset of their condition could not be determined. Of these, there were 15 psoriasis patients and 10 AD patients.

3.1.3 Demographic Details

Basic statistics for the patient groups, relating to their ages, are given in Table 1 (p53). Many more psoriasis patients than AD patients or controls presented at the clinics, in a ratio of approximately 2:1. Balancing of the numbers in each group was not done, since all patients who attended the clinics in the 18 month period of the study, who had psoriasis or AD or both were examined. The male to female ratio was 0.5 for controls, 0.76 for AD, 0.83 for psoriasis and 0.80 for the groups with both psoriasis + AD (Ps + AD), indicating that fewer males were referred to the clinics, particularly in the control group. All patient groups had ages that were skewed to the right, but particularly so for AD which was significantly skewed to the right. This is further shown by the calculation that 75% of AD patients were below the age

of 26 years. Of psoriasis patients, 75% were over the age of 23 years. The controls ages matched those of the psoriasis patients, but were older on average than the patients with AD.

Figure 1 (p54) gives the age profile of the patients. This shows that, broken down into the age groups of 1-9 years, 10-19 years, 20-49 years and 50+ years; 17% of psoriasis patients are below the age of 20, compared with 53% of AD patients, 24% of controls and 33% of those with both conditions. Most patients ages were in the age category 20 - 40 years, with 45% of those with psoriasis, 46% of AD patients, 36% of controls and 47% of those who had psoriasis plus AD. Very few (2%) of AD patients were aged 50+ years, indicating the skewness (1.02) of the ages of AD patients. Of psoriasis patients there were 39% in the 50+ years category, while 40% of controls were in this category and 20% of the group with both psoriasis plus AD.

In these same age groups, the ages of onset of the conditions were compared, excluding controls for whom this is irrelevant. The results are given in Table 2 (p55), which demonstrates that 82% of AD patients have an onset of less than 10 years of age, consistent with AD being primarily a disease of childhood onset. Of psoriasis patients, only 17% had an onset of less than 10 years. Also, 25.6% had an onset of the disease after the age of 50 years, compared with 0% of the group with AD. The group with both (Ps + AD) had a more indefinite onset as this was taken as the start of having skin problems, which was usually AD, since this has the earlier onset on average (See Table 4, p57). Of this group with both conditions, 2 (4.4%) had onset of dual pathology after the age of 50 years. Missing values here were those whose age of onset could not be determined, even in broad categories.

TABLE 1

Basic statistics of the ages of patients in each patient group and the ratio of males to females

PATIENT GROUP	n	MALE TO FEMALE RATIO	AGE (years) MEAN	MEDIAN	S.D.	RANGE	SKEWNESS	LOWER QUARTILE	UPPER QUARTILE
Ps	428	0.83	41.8	40.0	21.5	0 - 89	0.14	23	59
AD	224	0.76	19.2	19.0	14.9	0 - 81	1.02*	7	26
CONTROLS	286	0.50	42.5	42.5	24.1	0 - 96	0.05	20	63
AD + Ps	45	0.80	29.9	24.0	21.8	1 - 76	0.32	10	48

FIGURE 1

Histogram of the percentage of each type of patient, psoriasis (Ps), AD, psoriasis plus AD (BOTH), and controls (CONT), in each age category

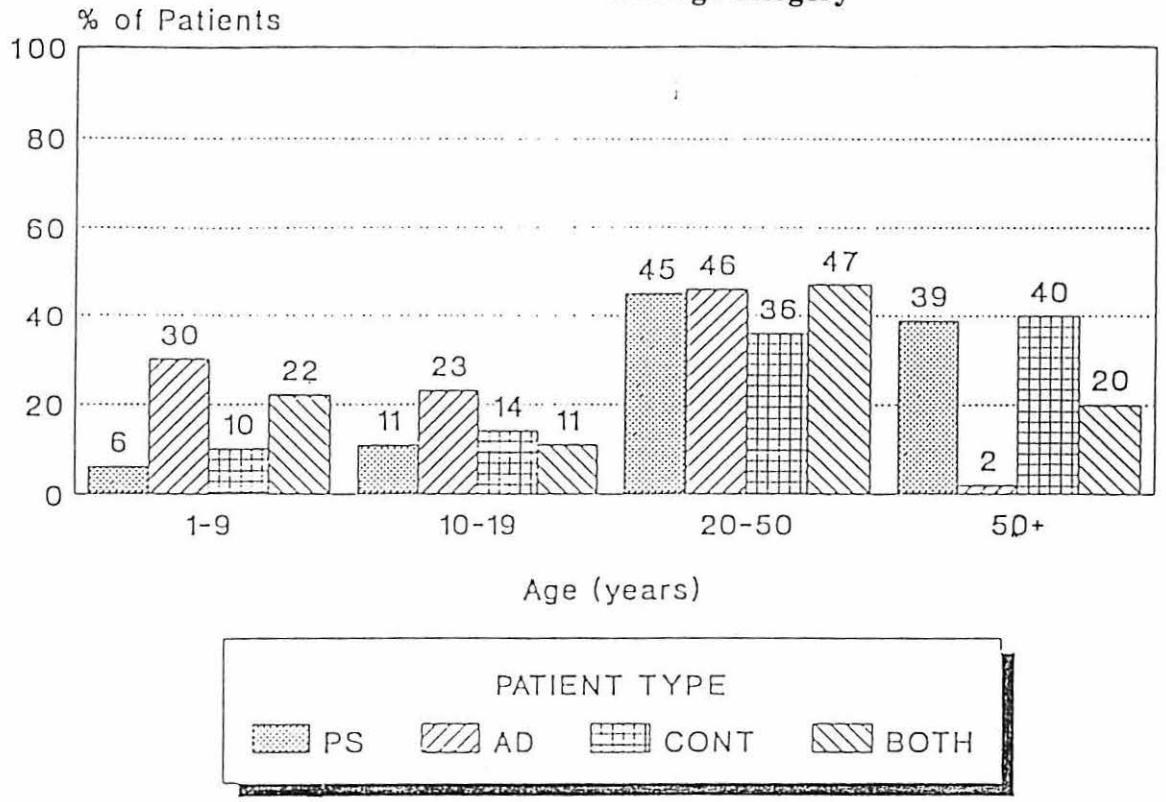


TABLE 2

Number of psoriasis (Ps) and AD patients in age of onset groups

Age of onset (years)	**Ps** n (%)	**AD** n (%)
< 10	71 (17.1)	176 (82.2)
10 - 19	101 (24.4)	26 (12.1)
20 - 49	135 (32.9)	12 (5.6)
50+	106 (25.6)	0 (0.0)
missing values	15	10
totals	428	224

3.1.4 Main Results of the Patient Examination

Of psoriasis patients, **9.5%** [45/(428+45)] had AD at some time, either concurrently or in the patient's past history. Of AD patients, **16.7%** [45/(224+45)] had psoriasis at some time. Of the patients who had both conditions (45), three quarters had psoriasis plus atopic lesions at the time of clinical examination.

The concomitance of asthma and hay fever occurring in the patients is recorded in Table 3 (p56). This was the presence of these conditions either concurrently or in the patient's history.

TABLE 3

Percentage of atopic conditions in the patient groups

for psoriasis (Ps), AD, psoriasis plus AD (Ps+AD) and controls (C)

	Ps	AD	Ps+AD	C
Asthma	9.3%	47.8%	37.8%	6.3%
Hay fever	10.0%	40.2%	42.2%	13.6%

There is a significant difference in the prevalence of asthma between the psoriasis patients and controls ($p < 0.05$). However, there is no significant difference between psoriasis patients and controls in the prevalence of hay fever ($p = 0.07$). There are no significant differences in asthma or hay fever, between the AD patient group and those patients with psoriasis plus AD (both $p > 0.05$). The AD patients and the psoriasis plus AD patients are highly significantly different from the psoriasis patients and controls (all $p < 0.001$) with regard to the prevalence of these two conditions.

3.1.4.1 The group with both conditions

A table of those patients who had both psoriasis and AD (Ps+AD), giving extra clinical details where these were helpful, was constructed. This recorded the age of onset of both conditions where possible, from either the clinical examination, the patient's recall or the patient's notes. Results are presented in Table 4 (p57). The definition of "Köbner Ps" was psoriatic plaques overlying dermatitis, usually in the antecubital and popliteal fossae. Numbers in brackets are age of onset.

Table 4 will be further examined in the discussion of results of the concomitance study, section 3.2.4.

TABLE 4
Clinical details of the 45 patients with dual pathology

No.	Sex	Age	Age of Onset of AD and Ps	Remarks
1	M	2/12	Simultaneous(2/12)	Large Ps plaques scalp, behind knees, axillae. Atopy in family
2	F	3/12	Simultaneous(3/12)	Ps plaque behind scalp, persisted 1 year. AD and Ps in family
3	F	1	Simultaneous(1)	Ps plaques on scalp and trunk. Atopy in family
4	M	14/12	Simultaneous(14/12)	Ps plaques left arm and perineum. Atopy and Ps in family
5	M	2	AD(Birth)→ AD+Ps(2)	Scaly Ps plaque vertex. Atopy in family
6	F	2 1/2	Simultaneous(2)	Heavy scalp scaling. Ps plaques on trunk and behind knees. Ps in father
7	F	5	Simultaneous(2)	Köebner Ps (popliteal fossae)
8	M	6	AD(birth)→ AD+Ps(6)	Atopy and Ps in family
9	M	9	AD(6wks)→ AD+Ps(8)	Atopy in family
10	M	9	Simultaneous(7)	AD and Ps in father
11	M	10	Simultaneous(10)	Köebner Ps (axilla and antecubital fossae).
12	M	12	AD(3)→ AD+Ps(12)	Ps in Mother
13	M	16	AD(birth)→ AD+Ps(16)	
14	F	16	Simultaneous(15)	
15	F	16	AD→ AD+Ps(16)	
16	F	18	AD(6/12)→ AD+Ps(18)	AD and Ps in family
17	F	18	Consecutive AD(2/12)→ Ps(18)	AD and Ps in family
18	F	20	AD(birth)→ AD+Ps(20)	
19	F	20	Consecutive AD(3/12)→ Ps(9)	
20	F	20	Ps(16)→ AD+Ps(18)→ Ps	Severe AD in family Patient - atopy (<10) Eczema - antecubital and popliteal fossae for a short period
21	M	20	AD(8)→ AD+Ps(20)→ AD	Köebner Ps - dorsa hands
22	F	22	AD(16)→ AD+Ps(22)	
23	M	24	AD(<10)→ AD+Ps(19)→ AD	
24	F	24	AD(6/12)→ AD+Ps(20)→ AD	
25	M	24	AD(<10)→ AD+Ps(>20)	
26	F	27	AD(<10)→ AD+Ps(27)	AD and Ps in family
27	F	30	AD(14)→ AD+Ps(?14)	
28	F	30	AD(<10)→ AD+Ps(30)	Asthma, allergies + +
29	F	32	Consecutive AD(<10)→ Ps(32)	
30	M	33	AD(<10)→ AD+Ps(32)	AD in brother. Ps in mother
31	M	36	AD(<10)→ AD+Ps(30+)	Flexural Ps. Vitiligo
32	F	38	AD(<10)→ AD+Ps(38)	
33	M	39	AD(<10)→ AD+Ps(34)	
34	M	45	AD(<10)→ AD+Ps(30's)	Asthma + +. Vitiligo
35	F	46	AD(<10)→ AD+Ps(40)	Asthma. Ps arthritis. Alcoholic

TABLE 4 (CONT)

36	M	50	Consecutive AD(2)→ PS(45)	Asthmatic
37	F	51	PS(?onset)+AD(30)	Ps scalp, trunk, perineum. Scaly scalp from childhood
38	F	54	AD(<10)→ AD+Ps(10-19)	Asthmatic. Ps in family
39	M	54	AD(46)→ AD+Ps(46+)	Eczema. Recurrent in popliteal fossae and soles. IgE 120ku/l. Asthma and eczema in family
40	F	60	Consecutive AD(<10)→ Ps(>20)	Ps in Mother
41	M	60	AD<10+Ps(?onset)	Köebner Ps(antecubital fossa). Ps nail changes
42	M	63	AD(50+)→ AD+Ps(50+)	Severe obstructive airways disease + eczema with lichenification. Ps about same time. Dry skin from young. IgE 1000 ku/l
43	F	64	AD(53)→ AD+Ps(60)	Lichenified eczema on wrists, ankles, dorsa feet. Vitiligo. IgE 124ku/l. Asthma and hay fever. Atopy in family
44	M	66	AD(27)→ AD+Ps(65)	On calcium antagonists
45	M	77	AD(<10)→ AD+Ps(40's)	Ps cleared. Recurred age 73. IgE 1856 ku/l. Hay fever in son. Ps in sister

3.1.5 Family History

The family history of psoriasis, AD, asthma and hay fever was recorded. The percentages of those who had at least one first degree family member with the condition were calculated.

The results are presented as a histogram in Figure 2 (p60). This demonstrates a close "matching" of the conditions diagnosed, in the patients, with the family incidence. Of psoriasis patients, 40% had psoriasis in the family, compared with 10% of AD patients and 9% of controls, both significantly different ($p < 0.001$). Of AD patients, 50% had a family history of AD compared with 16% of psoriasis patients and 14% of controls, both significantly different ($p < 0.001$). Of AD patients, 40% had asthma and 41% had hay fever in the family, compared with 20% and 16% respectively of psoriasis patients and 19% and 19% respectively of controls, all significantly different from the AD patients ($p < 0.001$).

3.1.5.1 The group with both conditions

The familial association of those patients with both conditions were compared to those who had been diagnosed as having "pure" psoriasis or "pure" AD. In this psoriasis plus AD patient group, a family history of psoriasis (36%) is not significantly different ($p = 0.30$) from the "pure" psoriasis group (40%). (Figure 2)

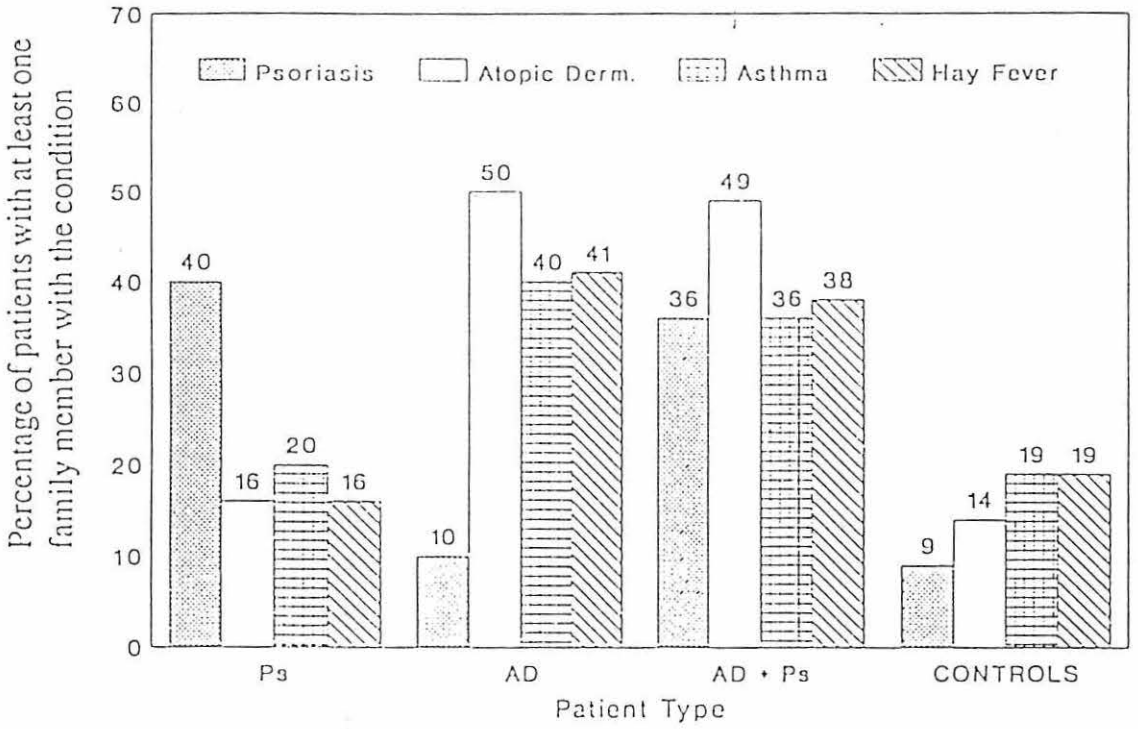
Similarly, a family history of atopic disorders in the psoriasis plus AD patient group is almost as common as in the "pure" AD group: of this group, 49% had AD in the family compared with 50% for "pure" AD. These are not significantly different ($p = 0.45$).

Of the patient group with both psoriasis plus AD, 38% had hay fever present in the family compared to 41% in the group with AD only, which is not significantly different ($p = 0.35$). Also, 36% of the group with both conditions had asthma in the family compared with 40% in those patients with AD only, not significantly different ($p = 0.30$).

Because of the importance of these results, and for further clarification of Figure 2, they are emphasised in Table 5 (p61), where the probabilities of getting the

FIGURE 2

Histogram of percentage of patients in each patient group with at least one family member with psoriasis (Ps), AD, asthma or hay fever.



results are given for the 2 groups under consideration. None are significantly different.

TABLE 5

Family history of psoriasis (Ps), AD, hay fever and asthma in the patient groups

Family History	Ps+AD	Ps	AD	p-value
Ps	36%	40%	-	= 0.30
AD	49%	-	50%	= 0.45
Hay fever	38%	-	41%	= 0.35
Asthma	36%	-	40%	= 0.30

3.1.5.2 Comparison of psoriasis patients and controls - incidence of atopy in the family

There are no significant differences in the incidence of the atopic conditions in the first degree relatives between psoriasis patients and controls. Figure 2 (p60) demonstrates that 16% of psoriasis patients have a family history of AD, compared with 14% of controls, which are not significantly different ($p = 0.23$). Likewise, 20% of psoriasis patients have a family member with asthma, compared with 19% of controls, which are not significantly different ($p = 0.37$). Hay fever is present in the family in 16% of psoriasis patients and in 19% of controls, again not significantly different ($p = 0.15$).

3.1.5.3 Comparison of AD and controls - incidence of psoriasis in the family

There were no significant differences between the presence of psoriasis in the families of those with AD and in the families of controls: of AD patients, 10% had psoriasis in the family whilst 9% of controls had a family member with psoriasis, which are not significantly different ($p = 0.35$).

3.1.5.4 Prevalences of psoriasis and AD in the family, using controls as estimators of the population

The controls are those patients without psoriasis or AD present, they would therefore be expected to give a slightly reduced prevalence of both psoriasis or atopy in their families. The total number of relatives of the controls was 1603, in which the family prevalences were (a) 26 out of a total of 1603 **(1.6%)** for psoriasis and (b) 46 out of a total of 1603 **(2.9%)** for AD. The author corrected for the missing psoriasis and AD in the controls by developing the following adjustments to these percentages:

(a) The prevalence of psoriasis in the relatives of psoriasis patients is 247 out of a total of 2443. If, using average British population estimates, 2% of controls would normally be expected to have psoriasis, there would be 2 x 283/100, that is, 5.66 psoriasis patients in the control sample of an average population. The mean number of affected relatives per psoriasis patient in this study is 247/413, that is, 0.598, and 5.66 patients would have 3.4 affected relatives on average. This means that the controls would have (26+3)/1603 relatives with psoriasis if psoriasis patients were included. This leads to an estimate of 1.8% of the population, from which this study's sample was drawn, having psoriasis.

(b) The figures for AD are:- 162 relatives affected with AD out of a total of 961. Using an average population estimate of 5%, there would be 5 x 283/100, that is, 14.1 AD patients in the control sample. The mean number of affected relatives per AD patient is 0.72. This gives an extra 10.2 affected relatives (14.4 x 162/223). The controls would have (46+10)/1603 relatives affected by AD. This leads to an estimate of 3.5% of the population, from which this study sample was drawn, having AD.

3.2 Discussion of dual pathology results

3.2.1 Groups Sizes

The imbalance in the sample sizes of psoriasis (428) and AD (224) patient groups possibly reflects the pattern of referral from general practitioners (G.P.s) to out-patient clinics in the U.K. It is believed that only the more severe AD patients are referred, those with a milder onset of the condition being dealt with by the G.P.s or by the patients themselves. A higher proportion of psoriasis patients seem to be sent for specialist treatment. There is an imbalance in the number of males and females in all patient groups, especially in the control group. This may be due to females being more concerned about skin conditions than men.

3.2.2. The Prevalence of Psoriasis Plus AD

The basic result of the study, that 9.5% of the psoriasis patients have had AD at some time and 16.7% of AD patients have / had psoriasis, shows that these two conditions are NOT mutually exclusive, over a patient's lifetime. Indeed it suggests that these patients have a higher prevalence of the other condition than would be expected in the population. Psoriasis prevalence estimates are approximately 2% (section 1.3.4), whilst AD prevalence estimates are approximately 5% (section 1.4.4). The corrected clinic sample estimates of the population are 1.8% for psoriasis and 3.5% for AD (section 3.1.5.4).

From these estimates from the clinic sample the patients with psoriasis have 2.9 times the risk of getting AD compared with the general population, that is, the odds ratio (O.R.) is 2.9 [95% C.I. = (0.94,8.8)]. Similarly, the AD patients have an O.R. of 10.9 [95% C.I. = (1.95,60.9)] with respect to psoriasis.

If the average population estimates are used instead of the estimation of prevalences from the clinics, the O.R. for a psoriasis patient with respect to AD, is 2.0 [95% C.I. = (0.77,5.2)]. Similarly, the AD patients have an O.R. of 9.8 [95% C.I. = (2.34,40.8)] with respect to psoriasis.

The prevalence of either psoriasis or AD in the Gwynedd population is not known. Such a "true" estimate would involve a large separate study. The "estimates" of the prevalence in the population, from the clinic sample for the two conditions are within reasonable levels compared with other studies (sections 1.3.4 and 1.4.4). It could be argued that these estimates are not representative of the population because only the most severe cases are normally sent to hospital clinics, however, all grades of severity of the two conditions are present, not just severe hospitalised cases.

If the two estimates of the population are considered to be two independent events, then by statistical reasoning, the probability of getting them together in a population sample would be the product of the two probabilities. For example, estimated probability of getting psoriasis [P(Ps)] is 0.018 and the probability of getting AD [P(AD)] is 0.035, then the probability of getting both in the population would be:-

$$P(Ps \cup AD) = P(Ps) \times P(AD)$$

that is

$$= 0.018 \times 0.035 = 0.00063$$

This means that one would expect to find approximately 6 in every 10,000 of the population have both psoriasis plus AD, at some stage in their lives, though not necessarily concurrent. However, this study examined, in the clinics, a small subsection of the population and found that 0.065 of the sample of all psoriasis and AD patients have both psoriasis plus AD.

Not only is there an apparent increase in AD amongst the psoriasis patients, but there appears also to be a large increase in psoriasis amongst the AD patients.

It could be argued that these percentages depend on the numbers in each group and that the 45 patients with both conditions come from the two groups combined. However, under the present method of referral and examination, if all the patients attending the clinic were examined for psoriasis first and then were examined closely for the presence of AD, the above number of psoriasis patients with

AD would be obtained, that is, a ratio of 45/473, or 9.5% of psoriasis patients with AD. Similarly, if all the patients were examined for AD, the above figures would have been obtained, that is 45/269, or 16.7% of the AD patients had psoriasis.

A hypothesis was formulated to try to explain the apparent increased prevalence of these patients with dual pathology.

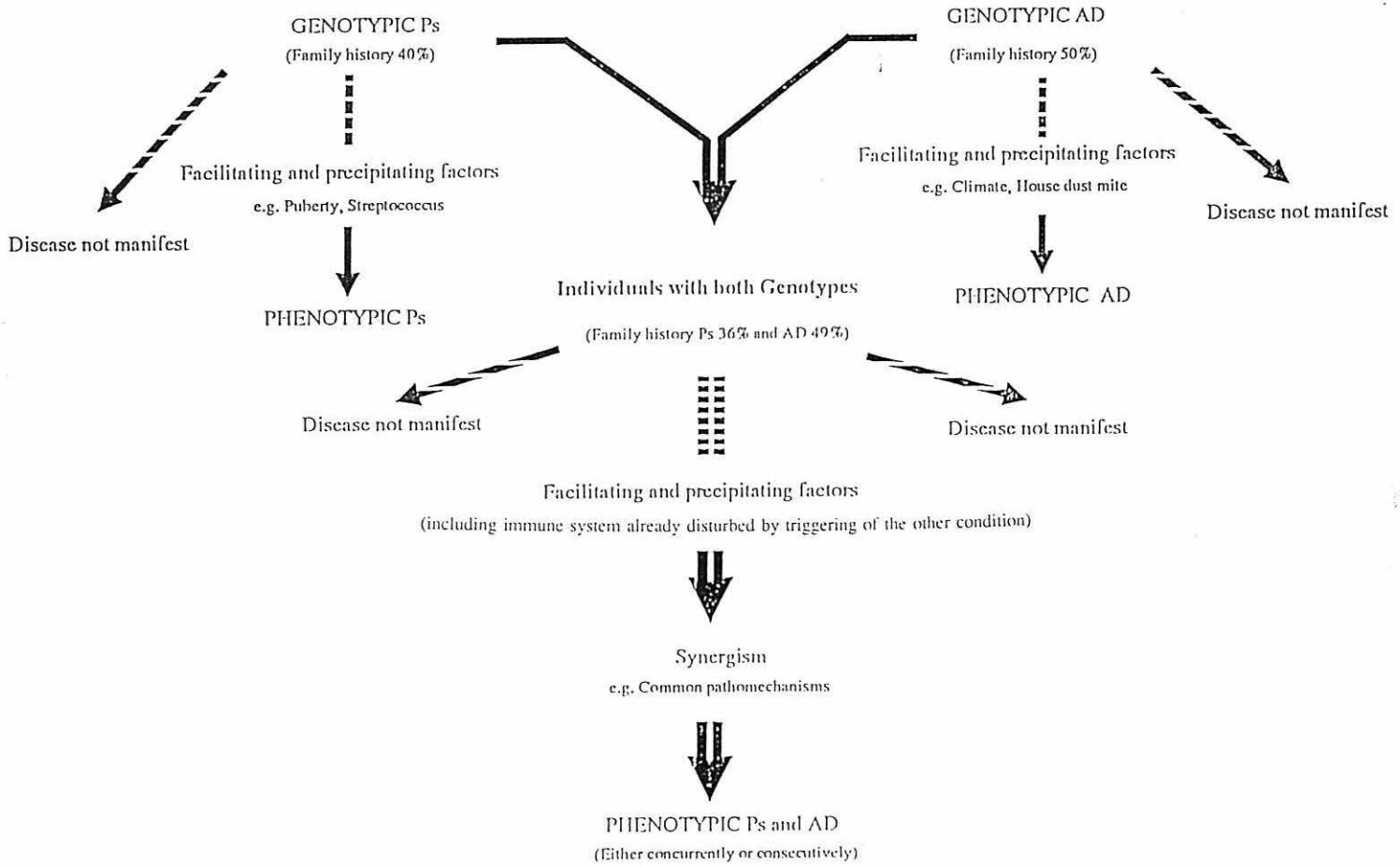
3.2.3 Hypothesis for the Basic Results of the Concomitance Study

A diagram of the familial incidences and the possible factors involved is presented in Figure 3 (p66). This makes the statement that those with the dual genetic predisposition, that is, both psoriasis and AD present in the family, have an enhanced susceptibility to the other condition after one of the conditions has been "triggered". A disturbance in the immune system, plus common pathomechanisms would create the conditions favourable to the expression of the other condition, although not necessarily at the same time. (This will be discussed further in section 3.2.4). Both psoriasis and AD patients show altered immunological response, which could make individuals with these conditions more vulnerable to other similarly triggered diseases.

This hypothesis is presented on the assumption that this study's figures demonstrate an increased concomitance of the two conditions, rather than any peculiarity in the population in Gwynedd. If the "estimates" of the population from controls are grossly wrong and the "true" prevalences in the population are much higher, then it could only be concluded that the two diseases are at least NOT mutually exclusive. Misdiagnosis or using different nomenclature according to the personal preference of the clinician, can lead to changed prevalences, for example when is psoriatic eczema called psoriasis plus atopic dermatitis? A hospital based study can mean that there is a bias towards certain types of patient when referrals come from other clinics with related conditions, for example chest clinics referring atopic patients. All these reflect local conditions, giving rise to possible assumptions of disease association when in fact there is only disease co-existence.

FIGURE 3

A hypothesis to explain the higher than expected concomitance of psoriasis and AD



3.2.4 Clinical Pattern in Those with Dual Pathology

In this study, a **concurrence** of severe psoriasis and severe AD in the same individual was not observed, although a combination of severe psoriasis and severe nummular eczema was encountered in an individual, who had a raised IgE, but since this patient lacked conclusive features of AD, the individual was excluded from the series. The ratio of concurrence to consecutive incidence of the two conditions in the patients was approximately 3:1.

The 45 patients with dual pathology showed features considered to be typical of each condition, such as early onset for AD especially affecting the face followed later by lichenification of the flexures (Table 4, p57). Generally, with this early onset the prognosis was towards improvement of their condition, with fewer relapses than average. The onset of psoriasis in younger children was concurrent with AD and demonstrated distinct scalp plaques with some circumscribed erythematosquamous lesions on the trunk and limbs. These psoriatic lesions on the scalp were slower to clear than lesions elsewhere. Of the consecutive cases, psoriasis manifested itself in adulthood, when AD was quiescent.

AD seemed to have been the more predominant condition, whilst psoriasis was more transient than typical for "pure" psoriasis patients. This is possibly demonstrating the influence of one condition over the other, or alternatively, it could result from the corticosteroid therapy applied for AD.

Sometimes one disorder masked the other, as in the case of a young woman with very severe unresponsive psoriasis affecting the scalp, trunk and limbs quite extensively (Table 4, case 20). She belonged to a family which was severely affected by AD in several members. Her psoriasis was almost totally unresponsive, if not made worse by psoriasis therapy of conventional type. She eventually benefited from topical steroids. It was only then that an underlying moderately severe xeroderma with flexural eczema became evident, indicating that the psoriasis was being made worse by the underlying AD.

3.2.5 Family History

The first degree family history of psoriasis, AD, asthma and hay fever was tabulated as this was thought to be a vital indicator of the validity of diagnosis, particularly for those patients who had psoriasis plus AD, indicating a familial predisposition to these conditions or not. The incidences, in the family for psoriasis and AD separately, are in broad agreement with those found by other researchers (section 3.1.1).

There is close positive matching of the group with both psoriasis plus AD, and the groups with psoriasis only or AD only, with regard to the incidences in the family of psoriasis or atopy respectively, when at least one family member is involved. (Figure 2 and Table 5, p60 & p61). This is mirrored by close negative matching, on the one hand between psoriasis and controls in that their family incidences of the atopic disorders are relatively infrequent, and on the other hand, there is an infrequent incidence of psoriasis in the families of AD patients as well as in the families of controls.

All these matchings in the family show that the familial element is as strong in those with dual pathology as in those with the separate diseases. These results, plus the fact that there is a similar matching for atopy in the patients themselves (Table 3), lends credence to the diagnoses of the patients with both conditions.

3.2.6 Other Studies on Dual Pathology of Psoriasis and AD

3.2.6.1 Those whose research indicates mutual exclusiveness

The main study which has reported findings in contrast to this study is that of Christophers and Henseler (1987), who carried out a retrospective study of 29,159 hospitalised patients from patient records for the period 1953-1983 at a hospital in Kiel, Germany. Of these they found that 2,467 (8.5%) had psoriasis, 470 (1.6%) had AD and found only 2 (< 0.1%) patients recorded as having both conditions together.

They also found that 30% of AD patients had infections compared to only 6.7% of psoriasis patients. On the basis of other researchers' estimates of prevalence rates for both diseases (Braun-Falco, 1968; Christophers and Krueger, 1987), they would have expected to find 30 (0.14%) prevalence of both conditions in their hospital population. From this they concluded that "mutual exclusiveness of Ps and AD as well as differential susceptibility to concomitant infectious diseases may be related to opposing mechanisms".

Among the drawbacks of the study by Christophers and Henseler was that all their patients were severe cases of either psoriasis or AD. It is possible that any minor features of the other condition were masked in their patients, since this present study did not find both pathologies occurring **concurrently** in severe forms. Alternatively, the features in their study could simply have been missed in the urgency to treat the patient for the main presenting condition. Furthermore, the study was a retrospective one, from notes done by many clinicians which could introduce subjective differences in diagnostic techniques. No account was taken of **consecutive** occurrences of the two conditions, thus eliminating patients in this category. This present study indicates that one quarter of the patients with dual pathology are in this category (section 3.2.4).

Others have agreed strongly with Christophers and Henseler: Dhar et al (1993) stated that in their study of 100 AD patients at a paediatric clinic in India, they could find no existing psoriasis. Similarly, in 112 psoriasis patients at this same clinic, no AD was found. They suggested that this indicated mutual exclusiveness. However, a contradictory statement was then made; "coexistence of these two diseases is entirely a relative phenomenon depending on genetic and environmental factors as well as the overall incidence of the diseases in the population studied".

It is, however, especially in children where AD is more severe, that minor psoriatic lesions, on the scalp or elsewhere, may be missed and a definite diagnosis difficult to make. Also, as Beer (1993) pointed out, manifestations of these conditions may vary between temperate and tropical climates.

3.2.6.2 Those studies which do not indicate mutual exclusiveness

Garofalo et al (1989) reported on the relationship between psoriasis and AD in patients in a paediatric clinic in Bari, Italy. Of 589 psoriatic children, they found a history of AD in 24 (4.1%) of these. When they examined those with only inverted psoriasis 8/92 (8.7%) children had a positive history of AD. The atopic diatheses was present overall in 12.5% of these 589 patients, which the authors state is higher than the local incidence of atopy in Bari. This increased to 49% of those with inverted psoriasis, indicating more than a four fold increase on the local population prevalence.

In the discussion following this paper it was stated that "psoriasis can be triggered by AD". Others agreed with this and it was thought that fixed categories did not exist, for instance, between atopic and contact dermatitis or inverted psoriasis and atopic eczema, and that differential diagnosis is frequently difficult.

Welp et al (1989), in a retrospective study from patient's notes in a hospital in Germany, showed that 1.7% of psoriasis patients had AD **concurrently**, and was present in psoriasis patients to the same extent as in the population. They point out that their study may be flawed because it is retrospective, computer based and they may only have taken into account the dominant disease, ignoring milder evidence of the other. They concluded that, with more accurate documentation, they expected the association to be more frequently observed. They stated that the difference in typical ages of manifestation of psoriasis and AD, make **concurrent** lesions unlikely, since AD is primarily a disease of infancy and psoriasis is mostly post-pubertal in onset.

Williams and Strachan (1994), have examined the occurrence of eczema and psoriasis in Britain, using data on 9263 children collected by the National Child Development study (Shepherd, 1985). Of children having eczema it was noted that 1.4% also had psoriasis concurrently, compared to the 1% prevalence of psoriasis stated in their study. This gave a risk of 1.4 when a child already had eczema. They stated that eczema almost invariably meant AD in the data and concluded that

there was no evidence of the two conditions being mutually exclusive, and some evidence of an increased risk of getting one in the presence of the other.

3.2.7 Critical Analysis of the Present Study

3.2.7.1 Concomitance estimates

Why was concomitance found in the patients of the present study so much more commonly than in other studies? Firstly, the presence of both disorders was actively sought by structured questioning and a rigorously complete physical examination. (It is suggested that in a busy clinical practice, once the diagnosis of the presenting complaint has been made, attention is often focused on the associated signs and symptoms of the disease rather than an exhaustive methodical quest for features of another disease.) There is also, a general reluctance to assign two diagnoses to a patient. In contrast with most studies, this study recorded both concurrent and consecutive dual pathology of psoriasis and AD. In addition, several other studies have only recorded the presence of atopy in psoriasis patients, this study also recorded the presence of psoriasis in AD patients.

Was it possible that concomitance was over-diagnosed? This is unlikely for several reasons. Only unequivocal cases were included and the observer (W.E.B.) was a dermatologist with long clinical experience. The validity of the diagnosis is thought to be irrefutably shown by the pattern of the presence of the two conditions in the family, matching the conditions which were not significantly different between those with dual pathology and those with "pure" psoriasis or those with "pure" AD (Figure 2 and Table 5, p60 & p61). This was also supported by the pattern of the conditions which were significantly different between the "pure" psoriasis patients and the "pure" AD patients compared with controls (Figure 2).

Could concomitance have been under-diagnosed? It is possible, since equivocal cases were excluded and since psoriasis may not be manifest until an older age, and some cases classed as AD may yet develop psoriasis.

Is it possible that there is something in the gene pool of the population of Gwynedd that means that there are high prevalences of psoriasis and AD? This could be possible, but the estimate of the population from the prevalence of these in the families of the controls gives no indication that this is so. They are reasonable, if slightly low, when compared with population estimates elsewhere (section 1.3.4; section 1.4.4).

One of the main drawbacks in this study was that the researchers have not been able to follow the patients through a complete lifespan to get the true lifetime concomitance of the two conditions, and from this point of view a degree of underestimation is likely.

3.3 **Clinical features in the patient history and clinical examination**

3.3.1 Results

The results of the clinical features in both the **patient** history section and the clinical **examination** section of the questionnaire (Chapter 2, Appendix A), are given in Tables 6 to 9 (p74-p81). The clinical features of psoriasis patients are presented in Table 6 (a) and (b), in descending order of significant difference from controls. Similarly, the features of AD patients, which are significantly different from controls, are presented in Table 7 (a) and (b). The features of the group with both psoriasis plus AD are presented in Table 8 (a) and (b). For differentiation between those clinical features found to be significant for each condition, Table 9 gives a comparison of the z values for each feature, according to the patient category. Here, B = both conditions together, that is Ps+AD (because of Table size limitations), +ve means positively significant, -ve means negatively significant and n.s. means not significant.

The percentages of patients with the feature are given in the first column, the probability of getting this value, as compared with controls, was obtained from a 1-tailed test of significance, using proportions and measured against a standard normal distribution:-

$$z = (p_1 - p_2) \Big/ \sqrt{\frac{(1-p_1)p_1}{n_1} + \frac{(1-p_2)p_2}{n_2}}$$

Here z is in standard normal deviations from the mean, (3rd column of the Tables) and p_1 here is the proportion of patients with the feature, p_2 is the proportion of controls with the feature.

(The z-values have been used instead of the χ^2 test because they give "directionality" in a 1-tailed test, that is, show negative correlations, rather than just the significance of the difference.)

The Null hypothesis is	$H_0 : p_1 = p_2$
The Alternative hypothesis is	$H_1 : p_1 > p_2$

The resultant probabilities of getting the above result for each feature is given in the second column of the Tables.

Of the **psoriasis** patient features, 9 were highly significantly different from controls ($p < 0.001$). These were rash only itch, scaling within the ears, seasonal changes, retro/infra auricular intertrigo, dandruff, lichenification, severe generalised itch, nummular eczema and seborrhoeic dermatitis. The rest were significantly different ($p < 0.05$); periorbital shadowing, acrocyanosis, Dennie Morgan folds and hyperlinear palms, or not significant. Combination skin was significantly negatively correlated with controls ($p < 0.01$).

Of the **AD** features, 17 were highly significantly different from controls ($p < 0.001$). These were generalised severe itch, lichenification, seasonal changes, Dennie Morgan folds, animal hair intolerance, IgE > 80 ku/l, asthma, xeroderma,

TABLE 6 (a)

The percentage of psoriasis patients with each clinical feature and the z-value and the p-value of these features

significant feature	%	p=	z=
rash only itch	45.3	<0.001	15.80
scaling within the ears	44.9	<0.001	15.41
seasonal changes	36.3	<0.001	14.70
retro/infra auricular intertrigo	35.9	<0.001	13.52
dandruff	43.7	<0.001	11.34
lichenification	21.1	<0.001	4.86
generalised severe itch	8.8	<0.001	3.80
nummular eczema	2.3	<0.001	3.19
seborrhoeic dermatitis	7.3	<0.001	3.08
periorbital shadowing	5.2	<0.01	2.56
acrocyanosis	1.2	0.01	2.26
Dennie Morgan folds	5.2	0.03	1.93
hyperlinear palms	3.3	0.04	1.73

TABLE 6(b)

The percentage of psoriasis patients with each clinical feature and the z-value and the p-value of these features

not significant feature	%	p=	z=
asthma	9.6	0.07	1.49
all skin itch	2.5	0.10	1.31
hay fever	10.5	0.10	1.26
migraine	13.1	0.19	0.88
papular urticaria	4.0	0.23	0.75
hyperhidrosis	4.9	0.25	0.60
IgE > 80 ku/l	34.4	0.28	0.58
xeroderma	9.6	0.29	0.55
keratosis pilaris	9.4	0.39	0.27
animal hair intolerance	6.1	0.46	0.11
negative correlation			
combination skin	3.7	<0.01	-2.20
fine hair	5.6	0.17	-0.95

TABLE 7 (a)

The percentage of AD patients with each clinical feature and the z-value and the p-value of these features

significant feature	%	p=	z=
generalised severe itch	61.5	<0.001	16.20
lichenification	59.8	<0.001	14.67
seasonal changes	48.9	<0.001	14.09
Dennie Morgan folds	46.4	<0.001	12.60
animal hair intolerance	50.2	<0.001	12.19
IgE > 80 ku/l	78.3	<0.001	11.79
asthma	47.3	<0.001	11.30
xeroderma	47.8	<0.001	10.65
retro/infra auricular intertrigo	34.8	<0.001	9.91
scaling within the ears	27.7	<0.001	7.44
hay fever	40.2	<0.001	6.95
rash only itching	18.5	<0.001	6.94
periorbital shadowing	21.0	<0.001	6.86
dandruff	26.6	<0.001	4.91
hyperlinear palms	10.8	<0.001	4.29
whole skin itch	9.2	<0.001	3.94
keratosis pilaris	16.2	<0.001	2.96
nummular eczema	2.2	<0.01	2.25
papular urticaria	1.8	<0.05	2.13
acrocyanosis	1.2	<0.05	1.71

TABLE 7 (b)

The percentage of AD patients with each clinical feature and the z-value and the p-value of these features

not significant feature	**%**	**p=**	**z=**
fine hair	11.7	0.05	1.62
seborrhoeic dermatitis	4.5	0.11	1.25
hyperhidrosis	4.9	0.30	0.52
negative correlation			
combination skin	4.4	0.04	-1.77
migraine	8.4	0.18	-0.98

TABLE 8 (a)

The percentage of the group of patients who have psoriasis plus AD with each clinical feature, the z-values and p-values of these features

significant feature	%	p=	z=
scaling within the ears	52.3	<0.001	6.59
retro/infra auricular intertrigo	48.9	<0.001	6.24
IgE > 80 ku/l	75.0	<0.001	6.10
rash only itching	14.6	<0.001	5.55
lichenification	47.7	<0.001	5.36
seasonal changes	40.0	<0.001	5.34
generalised severe itch	46.3	<0.001	5.14
animal hair intolerance	40.0	<0.001	4.55
dandruff	44.4	<0.001	4.54
asthma	37.8	<0.001	4.38
hay fever	37.8	<0.001	3.23
Dennie Morgan folds	20.5	<0.001	3.14
xeroderma	28.9	<0.01	2.97
seborrhoeic dermatitis	20.0	<0.01	2.92
whole skin itch	12.2	<0.01	2.24
periorbital shadowing	11.1	<0.05	1.98

TABLE 8 (b)

The percentage of the group of patients who have psoriasis plus AD with each clinical feature, the z-values and p-values of these features

non significant feature	%	p=	z=
migraine	20.0	0.07	1.46
nummular eczema	4.4	0.08	1.44
hyperlinear palms	6.8	0.08	1.42
papular urticaria	2.2	0.12	1.18
fine hair	8.9	0.37	0.33
keratosis pilaris	9.1	0.47	0.07
acrocyanosis	0.0	0.50	0.00
negative correlation			
combination skin	0.0	<0.001	-4.94
hyperhidrosis	0.0	<0.001	-3.02

TABLE 9

Comparison of z-values in clinical features between psoriasis (Ps), AD, psoriasis plus AD (B) patient groups, and their significance for each condition. (P=psoriasis, A=AD, B=psoriasis plus AD in the last column)

feature	Ps	AD	B	Significance
rash only itch	15.80	6.94	5.55	all +ve
scaling within the ears	15.41	7.44	6.59	all +ve
seasonal changes	14.70	14.09	5.34	all +ve
retro/infra auricular intertrigo	13.52	9.91	6.24	all +ve
dandruff	11.34	4.91	4.54	all +ve
lichenification	4.86	14.67	5.36	all +ve
generalised severe itch	3.80	16.20	5.14	all +ve
nummular eczema	3.19	2.25	1.44	P,A +ve
seborrhoeic dermatitis	3.08	1.25	2.92	P,B +ve
periorbital shadowing	2.56	6.86	1.98	all +ve
acrocyanosis	2.26	1.71	0.00	P,A +ve
Dennie Morgan folds	1.93	12.60	3.14	all +ve
hyperlinear palms	1.73	4.29	1.42	P,A +ve

TABLE 9 (continued)

Comparison of z-values in clinical features between psoriasis (Ps), AD, psoriasis plus AD (B) patient groups, and their significance for each condition. (P=psoriasis, A=AD, B=psoriasis plus AD in the last column)

feature	Ps	AD	B	Significance
asthma	1.49	11.30	4.38	A,B +ve
whole skin itch	1.31	3.94	2.24	A,B +ve
hay fever	1.26	6.95	3.23	A,B +ve
migraine	0.88	-0.98	1.46	n.s
papular urticaria	0.75	2.13	1.18	A +ve
hyperdidrosis	0.60	0.52	-3.02	B -ve
IgE > 80 ku/l	0.58	11.79	6.10	A,B +ve
xeroderma	0.55	10.65	2.97	A,B +ve
keratosis pilaris	0.27	2.96	0.07	A +ve
animal hair intolerance	0.11	12.19	4.55	A,B +ve
combination skin	-2.20	-1.77	-4.94	all -ve
fine hair	-0.95	1.62	0.33	n.s

retro/infra auricular intertrigo, scaling within the ears, hay fever, rash only itching, periorbital shadowing, dandruff, hyperlinear palms and whole skin itch. Keratosis pilaris, nummular eczema, papular urticaria and acrocyanosis were significantly different ($p < 0.05$) compared with controls. The rest were not significantly different ($p > 0.05$).

The **psoriasis plus AD** group had 12 features which are highly significantly different from controls ($p < 0.001$). These were scaling within the ears, retro/infra auricular intertrigo, IgE > 80 ku/l, rash only itch, lichenificaton, seasonal changes, generalised severe itch, animal hair intolerance, dandruff, asthma, hay fever and Dennie Morgan folds. Significantly different features ($p < 0.05$) were xeroderma, seborrhoeic dermatitis, whole skin itch and periorbital shadowing. The rest were not significantly different from controls, apart from combination skin and hyperhidrosis which were highly significant in a negative correlation with controls ($p < 0.001$).

When comparing **psoriasis features** and **AD** features (Table 10, p83 & p84), the z values of the difference between the two patient groups are presented, along with their probabilities. Also given is an indication of whether they can be considered as a psoriasis (Ps) or an AD feature, according to the results of the study. Highly significant (h.s.) psoriasis features ($p < 0.001$) are:- rash only itching, scaling within the ears, retro/infra auricular intertrigo and dandruff, whilst seborrhoeic dermatitis was significantly different (s.) ($p < 0.05$). Highly significant AD features are:- lichenification, generalised severe itch, periorbital shadowing, Dennie Morgan folds, asthma, hay fever, IgE > 80 ku/l, xeroderma and animal hair intolerance. Significant AD features are:- hyperlinear palms, whole skin itch, keratosis pilaris and fine hair.

TABLE 10

A comparison of the difference of psoriasis (Ps) and (AD) clinical features, their z-values, p-values and significance for each condition. (P=psoriasis, A=AD in the last column)

feature	z=	p=	Significance
rash only itch	8.86	<0.001	h.s. (P)
scaling within the ears	7.97	<0.001	h.s. (P)
seasonal changes	0.61	0.27	n.s.
retro/infra auricular intertrigo	3.61	<0.001	h.s. (P)
dandruff	6.43	<0.001	h.s. (P)
lichenification	9.81	<0.001	h.s. (A)
generalised severe itch	12.40	<0.001	h.s. (A)
nummular eczema	0.94	0.17	n.s.
seborrhoeic dermatitis	1.83	<0.05	s. (P)
periorbital shadowing	4.30	<0.001	h.s. (A)
acrocyanosis	0.55	0.29	n.s.
Dennie Morgan folds	10.67	<0.001	h.s. (A)
hyperlinear palms	2.56	<0.01	s. (A)

TABLE 10 (continued)

A comparison of the difference of psoriasis (Ps) and (AD) clinical features, their z-values, p-values and significance for each condition.

(P=psoriasis, A=AD in the last column)

feature	z=	p=	Significance
asthma	9.81	<0.001	h.s. (A)
whole skin itch	2.63	<0.01	s.(A)
hay fever	5.69	<0.001	h.s. (A)
migraine	-0.1	0.46	n.s.
papular urticaria	1.38	0.08	n.s.
hyperhidrosis	0.08	0.47	n.s.
IgE > 80 ku/l	11.21	<0.001	h.s. (A)
xeroderma	10.10	<0.001	h.s. (A)
keratosis pilaris	2.69	<0.01	s. (A)
animal hair intolerance	12.08	<0.001	h.s. (A)
combination skin	-0.43	0.33	n.s.
fine hair	2.57	<0.01	s. (A)

3.3.2 Discussion

3.3.2.1 Features of psoriasis

The most significant clinical features of the **psoriasis** group (Table 6 (a), p74) are those with a z-value above 10. These are rash only itch, scaling within the ears, seasonal changes, retro/infra auricular intertrigo and dandruff, all of which are those which are considered to be specific features of psoriasis. Seasonal changes meant an improvement in the patient's condition in the summer when the skin was exposed to U.V. radiation. Lichenified psoriasis was present in 21% of the psoriasis patients, demonstrating that lichenification was not a feature specific to AD. (Others, Chapter 2 Appendix B, p42, have considered lichenification a BASIC feature of AD.) Seborrhoeic dermatitis and nummular eczema are thought to have an association with psoriasis and sometimes seborrhoeic dermatitis and psoriasis are difficult to differentiate. It is possible that some of the number of psoriasis patients responding to the category of severe and generalised itch (or pruritus), normally considered to be a feature of AD (Chapter 2, Appendix B), was subjective response from patients in complaint of the condition.

3.3.2.2 Features of AD

AD features have been prominent in discussion in the literature (Chapter 2, Appendix B), and the clinical criteria were drawn up with an emphasis on the features considered as relevant criteria by W.E.B. and C.M.E.R.P. Table 7 (a)(p76) gives the features found, in this study, to be significantly different from controls. All the highly significant features are comparable with other studies in Appendix B. Seasonal changes here usually indicated a worsening of the condition in hot humid weather, promoting itching. Dandruff had not been specifically reported as an atopic feature, but here may be part of an overall xeroderma, which others consider to be a feature of AD (Chapter 2,

Appendix B). Of the less significant features, papular urticaria and acrocyanosis have been reported to be features of AD. Other possible atopic features, such as fine hair, migraine and combination skin were not significant, or negatively correlated (Table 7(b), p77).

3.3.2.3. Features of those with dual pathology

The features of both **psoriasis plus AD** together (Table 8 (a) and (b), p78 & p79) show a moderation of the z-values for features normally considered to be part of one condition in the presence of the other. For example, in Table 9 (p80), the z-values are usually between that for "pure" psoriasis patients and that for "pure" AD patients, or less than the value of both.

When expressed as the corresponding percentages of the z-values, typical examples of features normally considered to be those of AD are - generalised severe itch - 8.8% (Ps), 61.5% (AD) and 46.3% (B); Dennie-Morgan folds - 5.2% (Ps), 46.4% (AD) and 20.5% (B); IgE >80 ku/l - 34.4% (Ps), 78.3% (AD) and 75.0% (B); xeroderma - 9.6% (Ps), 47.8% (AD) and 28.9% (B); animal hair intolerance - 6.1% (Ps), 50.2% (AD) and 40.0% (B). The patients with both conditions have lower corresponding percentages of the z-values than "pure" AD. It appears that the presence of psoriasis in these patients is reducing the manifestations of features of AD. Typical examples for the group with dual pathology, of those features normally considered to be a psoriatic feature are - rash only itch - 45.3% (Ps), 18.5% (AD) and 14.6% (B); scaling within the ears - 44.9% (Ps), 27.7% (AD) and 52.3% (B); retro/infra auricular intertrigo - 35.9% (Ps), 34.8% (AD) and 48.9% (B); dandruff - 43.7% (Ps), 26.6% (AD) and 44.4% (B). The presence of AD appears from this to be modifying some of the psoriatic features.

Generally, it is indicated from the percentages and the z-values that it is possible that the psoriasis and AD in these patients is in a less severe form than the average "pure" psoriasis or the average "pure" AD patient. This

concurs with the statement that severe forms of both conditions did not exist together in the group of 45 patients (section 3.2.4).

3.3.2.4 Summary of features

It is probably not meaningful in this context to say that the patients had at least one of the significant features, or more, for example of AD, because here there are 17 highly significant features for this condition. Multivariate analysis was ruled out as requiring too complex a model, with results that would be difficult to identify, or impossible to interpret. A experienced dermatologist would be able to draw his own clinical criteria from the tables given here. However, Table 10 (p83 & p84) gives a comparison of features and their probabilities between psoriasis and AD patients. This gives an indication of significantly different features compared with another inflammatory dermatosis, a positive control, rather than just negative controls, and may give a greater idea of clinical criteria, separately, for psoriasis and AD. The highly significantly different features which can be used for this are given in section 3.3.1 .

The patients were not asked about Streptococcal throat infections, known to be a common trigger for psoriasis and as such, a preceding throat infection could be helpful in diagnosing psoriasis. Psoriasis patients showed a significant increase in psoriasis in the family, whilst AD patients showed a significant increase in atopic conditions in the family (section 3.1.5). From these and the features above, the information could be tabled into psoriasis criteria and AD criteria:-

PSORIASIS CRITERIA

BASIC

Family history of psoriasis

Preceding streptococcal throat infection

Typical lesions (section 1.1.1)

Typical location (eg. elbows, knees, scalp)

Itching of rash only

Scaling within the ears

Retro/infra auricular intertrigo

Dandruff

MINOR

Seborrhoeic dermatitis association

AD CRITERIA

BASIC

Family history of atopy

Personal history of asthma, hay fever

Typical lesions (section 1.1.2)

Typical location (eg. flexures, face)

Generalised severe itch

Animal hair intolerance

IgE > 80 ku/l

Dennie Morgan folds

Xeroderma

Lichenification

Periorbital shadowing

MINOR

Keratosis pilaris

Fine hair

Hyperlinear palms

Whole skin itch (NOT severe)

CHAPTER 4

THE AGE OF ONSET IN PSORIASIS, AND ASSOCIATED RELATIVES

4.1 Introduction

While carrying out the study on the concomitance of psoriasis and AD, it was noted that clinicians had reported that, although the majority of psoriasis patients had an onset in early adulthood, a considerable number first had psoriasis in older age (Burch and Rowell, 1965; Gunawardena et al, 1978). The age of onset was specifically examined by Henseler and Christophers (1985) who found two age of onset distributions in hospitalised psoriasis patients, divided at the age of 40 years. They suggested that this indicated the existence of two types of psoriasis, based on the patient's age of onset and the familial association.

It was decided to examine the age of onset of the psoriasis patients in this study to see how they were distributed. The first part of this chapter deals with a detailed analysis of the ages of onset (Smith et al, 1993).

In the second part of this chapter the ages of the psoriasis patients, at the time of examination at the clinics, are analysed to see if this influenced the ages of onset distribution. For comparison with epidemiological studies, an iterative process was developed to give expected ages in the population (Smith et al, 1993).

It was then decided to look at the number of first degree relatives who had psoriasis, and see if any pattern emerged, especially in relation to the onset in the patient. A model was then developed for correcting for the cumulative numbers of relatives with increasing age in the patient, in order to standardise

the results. Contrasts between this study and that of Henseler and Christophers (1985) are discussed in relation to this. Finally, the clinical features of psoriasis in the early and late onsets are detailed.

4.1.1 Research Studies on the Age of Onset in Psoriasis

The general understanding on the age of onset of psoriasis, until recently, has been that psoriasis can appear at any stage in life, that is, a single distribution, although having a postpubertal typical onset. There has been little reporting of mixtures of distributions.

Romanus (1945) reported a median of the onset ages of 19.1 years for males and 12.5 years for females in psoriasis patients. Steinberg et al (1951) did not state a median but found that in 464 patients in the Mayo clinic in Rochester, U.S.A., the "average age at onset was 32 years for males and 28 years for females". The modal ages in their study were 20-29 years and 10-19 years respectively. Lomholt (1963), in a study of psoriasis in the Faroe Islands, found a median of 13 years for males and 12 years for females, with a mode at 5-9 years for both sexes. He suggested that exogenous factors, such as climate, were contributing to the "eruption of psoriasis".

The major epidemiological study carried out by Farber and Nall (1974) analysed the age of onset of 5,444 psoriasis patients in the U.S.A. into classes of 10 year intervals. This showed the onset as a single distribution with a mean age onset of 29 years for males and 26 years for females. The modal ages of onset were 20-29 years for males and 10-19 years for females. Similar findings had been reported in a sample of 2,099 ages of onset from a study carried out previously in the U.S.A. (Farber et al, 1968), where the mean age of onset in males was 28.7 years and 26.2 years in females.

Kononen et al (1985), in an epidemiological survey of 1517 psoriasis probands in Finland, reported a mean age of onset of 25.5 years in all those without psoriatic arthritis, but did not refer to two onset distributions. Karasek (1990) in a later article on the developments in the understanding of psoriasis,

did not mention the possibility of two onset groups, even though he discussed the genetics of the condition.

Morris (1989) fitted a plot to Farber & Nall's (1974) histogram of ages of onset in 5,444 psoriasis patients. He demonstrated that this fits in with a statistical decision theory that he had formulated previously to explain certain autoimmune diseases (Morris, 1987). This theoretical model states that "the age incidence of autoimmune diseases will be the result of two processes, one rising and one falling from birth". He suggests that the first process involves the hypothesis that those who are genetically predisposed to psoriasis have an increasing chance of error occurring in their immune system with increasing age. The second process uses the hypothesis that, in the patients, the age incidence of the contact with the trigger to the immunological process, decreases with age. The resulting single overall theoretical plot matches closely the age of onset histogram at 10 year intervals, with the plot reaching a peak in early adulthood and tailing off with increasing age.

Review articles continued, until very recently, to treat the age of onset of psoriasis as a single distribution, examples being Rowland Payne (1987) and Fry (1988). Fry stated that the disease is rare before the age of 3 years and quoted Radcliffe Crocker's (1903) report on psoriasis that indicated that two thirds of psoriasis patients had an age of onset before the age of 30 years, but it was possible to have an onset of psoriasis throughout life. Fry asserted that he thought these were still acceptable statements.

Some researchers, however, had indicated that there may be two onset distributions in psoriasis. Burch and Rowell (1965) reported on an "age pattern consistent with two distinct onsets" triggered by the "occurrence of a number of specific random events". They stated that this pattern was similar to other autoimmune processes (Burch, 1963). They identified two modes of onset for males at 15.5 years and an "erratic" peak at about 45 years, and for females at 11 years and also at 45 years, when they grouped their age of onset data into 5 year increments to construct their distributions. They suggested

that the resultant distributions may provide a "previously unappreciated complication for the interpretation of the familial evidence". Gunawardena et al (1978) in a study of 1,366 psoriasis patients in Sri Lanka reported the possibility of two distribution of ages of onset, but did not comment further on the consequences of this.

Henseler and Christophers (1985) and later, Christophers and Henseler (1989) postulated that there are two types of psoriasis: Type I being hereditary and of early onset and Type II being non-hereditary and of late onset. They had examined, retrospectively, 2,147 hospitalised cases of severe psoriasis and found that the data of age of onset could be represented by two distinct distributions, both approximately normal. When differentiated by sex, the peaks of the distributions occurred at 22 years and 57 years for males and 16 years and 60 years for females.

4.2 **Materials and methods**

4.2.1 The Data

Most of the data for this part of the study was obtained from the Gwynedd database described previously in Chapter 2. The patients had been grouped into age of onset classes of 1-9 years, 10-19 years, 20-49 years and 50+ years, until half way through collection of the data, the exact age of onset was recorded, if known, after the significance of Henseler and Christophers's (1985) research was noted. Confirmation of earlier patients' ages of onset was sought from clinical notes or from the patients themselves. This resulted in a subgroup of 328 psoriasis patients whose sole criteria for entrance into this part of the study was an exact age of onset. Of these patients, those relatives

who had psoriasis had usually attended the same clinics and were known to the dermatologist in Gwynedd, and so accuracy of reporting of the first degree relatives with psoriasis, was enhanced.

A second smaller sample of 128 cases of psoriasis from a different geographical area was gathered for comparison. These were obtained retrospectively from patients notes at out-patient clinics in Kent, over a 12 month period of referral to one dermatologist in Kent. Age and age of onset had been recorded. This Kent sample was analysed both separately from, and also in combination with, the larger prospective sample from Gwynedd.

4.2.2. Statistical Analysis Employed

The package SPSS-X™ (SPSS Inc., 1988) was employed to obtain basic statistics of the age and age of onset of psoriasis for the Gwynedd and Kent data for straight comparison purposes, to see if the two data sets were equivalent and whether there were differences between the sexes in terms of distribution. As a preliminary look at the data, the ages of onset were analysed using the package Minitab, with a Shapiro-Wilks test applied to see if the data was normally distributed overall. The method of Foulkes (1979) was then applied, using Minitab, as an initial step towards the detection of the possibility of the presence of a mixture of two distributions.

A more formal analysis was subsequently carried out on all the data by the method of maximum likelihood, using the statistical package MLP (Ross, 1980), available on the VAX mainframe computer. MLP contains statistical procedures for goodness of fit of distributions to standard distributions which uses an iterative method of least squares to estimate the values of the required parameters. It gives the estimates of the parameters which maximise the overall likelihood function (**L**),

where :-

$$L = f(\underline{x}\,;\,\underline{\theta})$$

and $\underline{x}$ and $\underline{\theta}$ are vectors of the data and the parameters, respectively. When the logarithm of **L** is used and the partial derivative of this with respect to $\underline{\theta}$ is taken, the maximum likelihood of $\underline{\theta}$ is obtained from the equation.

$$\frac{\delta \ln L}{\delta \underline{\theta}} = \underline{0}$$

The procedure requires that sample observations are assigned to classes to enable calculations of the probabilities associated with each class. These classes are chosen as appropriate by the user and it was decided to use 5 year intervals in the ages under consideration, as preliminary analysis indicated that this gave an optimum of sufficient numbers in each class with separation for identification of distributions. The multinomial distribution of these observed class frequencies about expected frequencies, forms the basis of the likelihood estimation of parameters. The residual log-likelihood provides a χ^2 test of goodness of fit with m-p-1 degrees of freedom where m is the number of classes, and p is the number of estimated parameters.

Various continuous models were fitted including univariate normal and double normal distributions and single negative binomial discrete distributions.

Generally, a univariate normal distribution is uniquely determined by μ the mean, and σ^2 the variance.

The density function for an double normal distribution by the method of maximum likelihood is of the form :-

$$f(x) = p\ \theta(x\ ;\ M_1\ ,\ S_1) \quad + \quad (1-p)\ \theta(x\ ;\ M_2\ ,\ S_2)$$

where θ is the probability density function, $\mathbf{M_1}$ and $\mathbf{M_2}$ are the means, and $\mathbf{S_1}^2$ and $\mathbf{S_2}^2$ the variances for individual distributions and where **p** and **(1-p)** are the proportions.

The negative binomial distribution generally is of the form:-

$$p(x\ ;\ k,\ p)\ =\ \binom{x-1}{k-1}\ p^{k}\ (1-p)^{x-k}$$

where **x = k, k+1, k+2** .....

in which **x** is the negative binomial random variable and is the number of Bernoulli trials required to produce a fixed number (**k**) of "successes". It is uniquely determined by the parameters, that is, **μ** the mean and **k** where $\sigma^2 = \mu/k(\mu + k)$ and the index of dispersion is $\sigma^2/\mu > 1$. A crude estimate of **k** can be obtained from samples by

$$k\ =\ \frac{\overline{X}^2}{(S^2\ -\ \overline{X})}$$

and the best estimate of **k** is obtained by the method of maximum likelihood.

The M L Program uses the density function for a negative binomial of the form:-

$$p(x)\ =\ \binom{x\ +\ k\ -\ 1}{k\ -\ 1}\ [M/(M\ +\ k)]^{x}\ [(1+M/k]^{-k}$$

where **M** is the mean, **k** the parameter as before.

4.3 **Results for age of onset in the patient**

4.3.1 Demographic Details

The ages of onset were known for 211 male psoriasis patients and 245 female psoriasis patients, with the Gwynedd and Kent samples combined. Of

these, 158 males were from Gwynedd and 53 from Kent, while 170 females were from Gwynedd and 75 from Kent. The basic statistics for the ages of onset of the combined Gwynedd and Kent samples for males and females separately, and their ages at the time of examination are given in Table 1 (p97). The mean age is approximately 9 years greater, in both males and females, than the mean age of onset. The means, medians and standard deviations between males and females, are all not significantly different ($p > 0.05$), for both ages of onset. The range of age of onset in males and females were comparable, as were the ages of male and females.

4.3.2 Preliminary Analysis of Ages of Onset

The package Minitab was used to analyse the ages of onset in psoriasis of male and female Gywnedd data combined and Kent male and female data combined, because of the apparent similarities in the distribution between males and females (Table 1) and to maximise numbers for testing. Histograms at 10 yearly increments were done for direct comparison with other studies (Farber & Nall, 1974) and also at 5 year increments (Figures A1 and A4, Appendix p145 & p148). The overall distributions were tested for normality using a Shapiro-Wilks test (Figures A2 and A5, p146 and p149). These demonstrated that the overall distribution was not normally distributed for both Gwynedd data and Kent data ($p < 0.05$).

A programme was written to emulate the method of Foulkes (1979) and applied to both distributions (Figures A3 and A6, p147 & p150). This gave more definitive visual evidence of a mixture of distributions being present, since a single distribution would have produced a horizontal straight line.

Histograms of males and females separately were produced for Gywnedd psoriasis onset data (Figure 1, p98) and Kent psoriasis onset data (Figure 2, p99). These indicated the presence of a minima at the class with mid point 42 years for both the Gwynedd male and female distributions and the Kent females, whilst the Kent males had zero frequencies at the onset classes

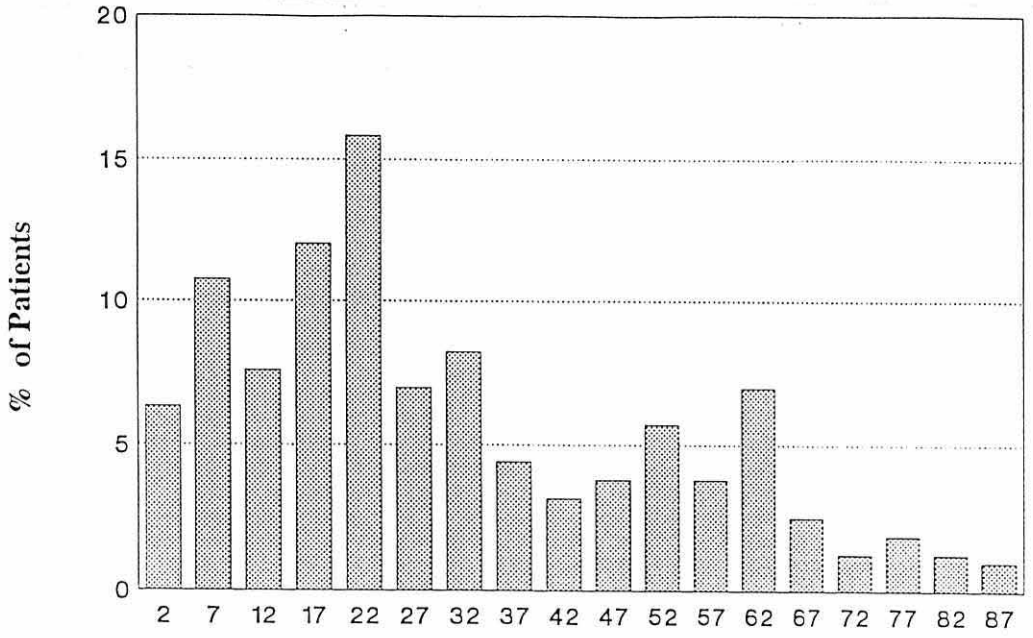
TABLE 1

Basic statistics for age and age of onset of male and female psoriasis patients, Gwynedd and Kent data combined

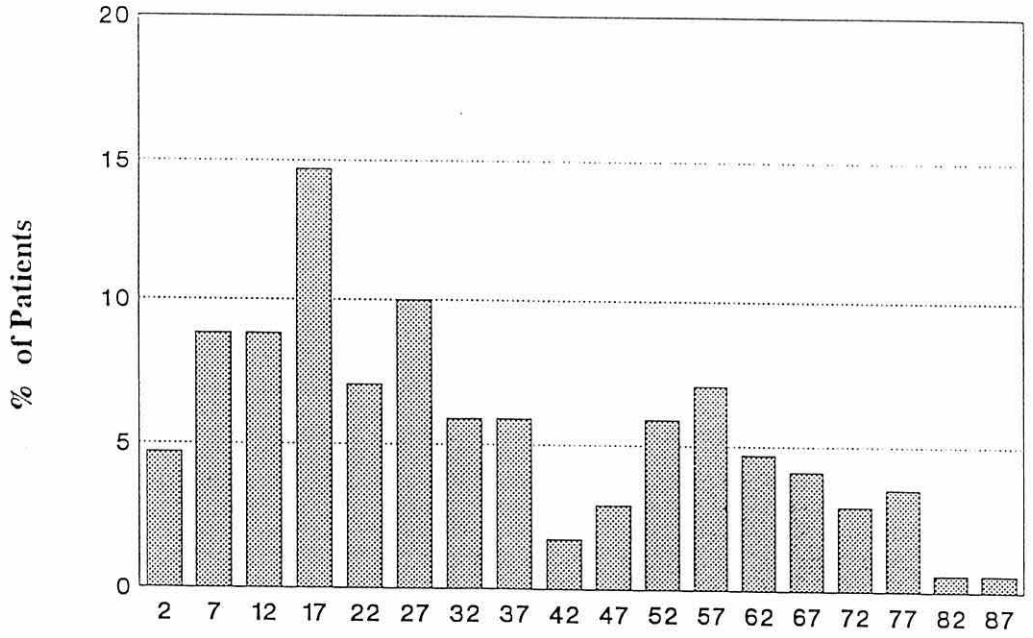
		n	Mean	Median	SD	Range	Lower quartile	Upper quartile
Age of onset	**Males**	211	31.4	25.0	20.7	1 - 87	16.0	47.0
	Females	245	32.9	26.0	22.0	1 - 89	15.0	53.0
Age	**Males**	211	40.3	40.0	20.2	1 - 87	23.8	54.0
	Females	245	41.7	39.0	21.7	1 - 89	23.8	58.0

FIGURE 1

Histogram of the percentage of psoriasis patients in each age of onset category - Gwynedd data, for both males and females



Male

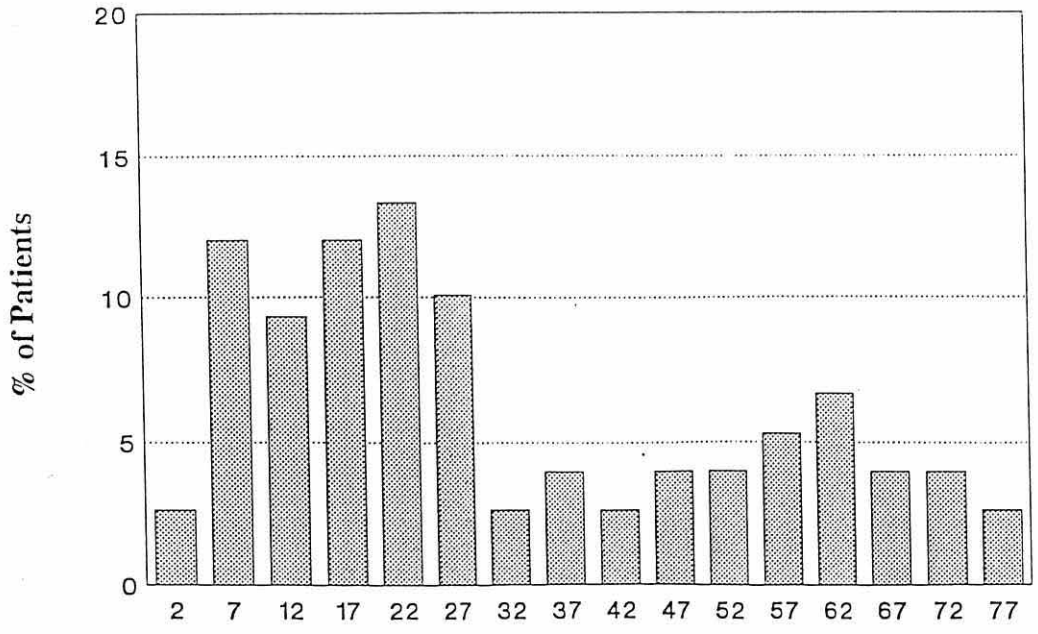


Female

FIGURE 2

Histogram of the percentage of psoriasis patients in each age of onset category - Kent data, for both males and females

Male



Female

with mid points 47 and 52. This was probably as a result of too few numbers in older onset Kent males in the sample.

4.3.2.1 Categorisation of ages of onset

A preliminary analysis of patients into two groups, the early onset and late onset psoriasis, with division at 40 years, was carried out because of the above results, and also because of the reporting of Henseler and Christophers (1985). Analysis of the individual male and female onset categories and the numbers in each, is given in Table 2 (p101). The proportion of numbers in the early onset to late onset categories in all groups was approximately 2:1 . The proportion of males to females in early onset group was not significantly different ($p = 0.17$), also the proportion of males to female in the late onset group was not significantly different ($p = 0.26$). Here, Q_1 and Q_2 are the lower and upper quartiles of the distribution and are similar over all categories. The modes were determined visually where possible from yearly increment histograms of the onset ages, except where lack of numbers prevented this. Overall, a mode of 21 years was found for males of early onset which was later than the mode for females of early onset, at 16 years. Similarly, a mode of 62 years was seen for males of late onset and a mode of 56 years for females. The variances were F-tested for any difference between males and females, for both the early onset group and the late onset group, and all were found to be not significantly different ($p > 0.05$). The means, in comparable ages of onset groups, when t-tested, were all not significantly different ($p > 0.05$). The means and medians were similar for comparable onset groups.

4.3.3 Analysis of Ages of Onset by Maximum Likelihood Estimation of Parameters.

The Maximum Likelihood Program (Ross, 1980) was applied to all groups of patients data of onset:- Gwynedd males, Gwynedd females, Kent males, Kent

TABLE 2

Basic statistics of the age of onset categories in psoriasis for males and females, and for Gwynedd patients and Kent patients and all patients

		n	Mean	Median	SD	Mode	Prop.	Q_1	Q_2
Gwynedd	**M <40 years**	111	19.5	20.0	10.1	20	0.70	11.0	27.0
	M >40 years	47	59.4	59.0	10.9	-	0.30	51.0	65.0
	F <40 years	111	19.7	20.0	9.8	20	0.65	11.0	27.0
	F >40 years	59	61.7	60.0	11.0	-	0.35	53.0	71.0
Kent	**M <40 years**	40	21.1	18.0	10.5	16.5	0.75	15.0	29.5
	M >40 years	13	62.1	64.0	10.3	-	0.25	57.5	69.0
	F <40 years	51	18.5	18.0	9.4	21	0.68	10.0	26.0
	F >40 years	24	60.3	61.0	9.3	-	0.32	52.5	66.5
All	**M <40 years**	151	19.9	19.0	10.2	21	0.71	12.0	28.0
	M >40 years	60	60.0	60.0	10.7	62	0.29	52.0	67.8
	F <40 years	162	19.3	20.0	9.7	16	0.66	11.0	26.0
	F >40 years	83	61.3	60.0	10.5	56	0.34	53.0	69.0

females as well as all males and all females. The sexes were examined separately, on the basis of females being demonstrated to have an earlier onset mode of 16 years compared with 21 years for males. The upper end classes had to be amalgamated to compensate for low frequencies in the older onsets, above the age of 75 years. The programme adjusted the amalgamations further, to accommodate for low frequencies. This resulted in lower degrees of freedom, for the original classes (m) and the parameters estimated (p), of m - p - 1.

A single normal distribution model, estimating the mean and standard deviation as parameters, was strongly rejected in all groups (Table 3).

TABLE 3

Maximum likelihood fits of ages of onset in psoriasis, for males and females, Gwynedd and Kent data and all data combined (single normal model)

Patient group	χ^2	**d.f.**	**p=**
Gwynedd males	53.77	15	<0.001
Gwynedd females	55.95	15	<0.001
Kent males	35.70	13	<0.001
Kent females	34.12	13	<0.001
All males	64.30	13	<0.001
All females	78.76	13	<0.001

The data was tested for a mixture of distributions by using three double normal models to estimate 3,4 and 5 parameters respectively, where $\mathbf{M_1}$ and $\mathbf{M_2}$ are the means of the first and second distributions.

Model A (S, 0.5, $\mathbf{M_1}$, $\mathbf{M_2}$) - equal proportions and equal variances, where 3 parameters are estimated, two means and a common variance. Here

the proportions of the first and second distribution are both 0.5 and **S** is the common variance.

Model B (S, p, M_1, M_2) - unequal proportions and equal variances where 4 parameters are estimated, two means, the proportion of the second (late onset) distribution, and the common variance. Here **p** is the proportion relating to the second distribution and by implication, **1-p** is the proportion of the first (early onset) distribution. **S** is the common variance.

Model C (S_1, S_2, p, M_1, M_2) - unequal proportions, unequal variances, where 5 parameters are estimated, two means, the proportion of the second distribution, and two variances. Here **p** is as for model **B**, S_1 and S_2 are the variances of the first and second distribution respectively.

Of these, the 3 parameter model, Model A, was rejected in all groupings of patients, that is, the model was significantly different from the data ($p < 0.05$), except for Kent females* where this was not significantly different ($p = 0.26$), but was the poorest fit of the three models.

TABLE 4

Maximum likelihood fits of ages of onset in psoriasis, for males and females, Gwynedd and Kent data and all data combined (3 parameter model)

Patient group	χ^2	d.f.	p=
Gwynedd males	38.66	14	<0.001
Gwynedd females	28.35	14	0.01
Kent males	33.53	12	<0.01
Kent females*	14.71	12	0.26
All males	47.16	12	<0.001
All females	35.95	12	<0.001

The results of applying the 4 parameter model (Model B) are given in Table 5 (p105) and the results of applying the 5 parameter model (Model C) given in Table 6 (p106). These are given in full, along with the calculated 95% confidence intervals (CI) for each onset group, as the results between the two models are only marginally different. (Abbreviations used in the tables are (G) = Gwynedd, (K) = Kent.)

Overall Model B gave the best fits, where equal variances but unequal proportions between the two distributions were assumed. In all cases the ratio of early onset to late onset was approximately 2:1. Best fits were obtained for all the female groups using Model B. Best fits were obtained for the groups of Kent males and all males together using Model B. However, the best fit for Gwynedd males* was found using Model C, the 5 parameter model with unequal variances ($\chi^2 = 14.15$ with 10 d.f., $p = 0.17$.

Overall the confidence intervals gave good separation of the mixture of two distributions with little overlap, indicating strongly two separate normal distributions being present. The exception was in Gwynedd males where the 5 parameter model, Model C, for the data gave a larger overlap at the extremities of the confidence intervals than the Model B fit (1-38 ; 28-84 compared with 0-43 ; 38-81). However, the confidence intervals for all males distribution and for all females distribution strongly suggested that there was a separation of early and late onset distributions at the age of 40 years.

A histogram for all male ages of onset with the fitted maximum likelihood plot (4 parameter model) superimposed is given in Figure 3 (p107). Similarly, a histogram for all female ages of onset with maximum likelihood plot superimposed is given in Figure 4 (p108). These indicated good overall fits for both the female data and for the male data. Modal values for the fitted distributions were 21 years and 62 years for males and 17 years and 57 years for females.

TABLE 5

Maximum likelihood fits of ages of onset in psoriasis for males and females, Gwynedd (G) and Kent (K) data and all data combined (4 Parameter Model)

	Younger onset					Older onset							
	n_1	Propor -tion p	M_1	S_1	95% CI	n_2	Propor -tion p	M_2	S_2	95% CI	χ^2	df	p-value
males (G)*	111	0.70	20.5	10.8	0 - 43	47	0.30	59.5	10.8	38 - 81	16.16	11	0.14
females (G)	112	0.66	19.7	11.2	0 - 42	58	0.34	61.2	11.2	39 - 83	11.84	11	0.38
males (K)	39	0.74	20.7	10.8	0 - 42	14	0.26	60.0	10.8	39 - 81	5.76	3	0.12
females (K)	51	0.68	18.5	10.7	0 - 39	24	0.32	60.9	10.7	40 - 82	1.17	3	0.76
all males	142	0.68	19.9	10.0	0 - 40	69	0.32	60.3	10.0	41 - 80	13.74	11	0.25
all females	163	0.67	19.5	10.8	0 - 41	82	0.33	61.0	10.8	40 - 82	12.10	11	0.36

TABLE 6

Maximum likelihood fits of ages of onset in psoriasis for males and females, Gwynedd (G) and Kent (K) data and all data combined (5 Parameter Model)

	Younger onset					Older onset							
	n_1	Propor -tion p	M_1	S_1	95% CI	n_2	Propor -tion p	M_2	S_2	95% CI	χ^2	df	p-value
males (G)*	103	0.65	19.2	9.5	1 - 38	55	0.35	56.0	14.3	28 - 84	14.15	10	0.17
females (G)	110	0.64	19.1	10.5	0 - 40	60	0.36	59.3	12.9	34 - 85	11.20	10	0.34
males (K)	43	0.81	22.9	10.8	2 - 44	10	0.19	65.7	7.2	52 - 80	5.65	2	0.06
females (K)	50	0.67	18.3	10.2	0 - 38	25	0.33	60.4	11.5	38 - 83	1.05	2	0.60
all males	142	0.68	19.9	10.0	0 - 40	69	0.32	57.6	13.4	32 - 84	12.73	10	0.24
all females	160	0.64	18.9	10.0	0 - 39	85	0.36	59.6	12.5	35 - 84	10.91	10	0.36

FIGURE 3

Histogram of percentage of male psoriasis patients in each age of onset category, with maximum likelihood plots superimposed

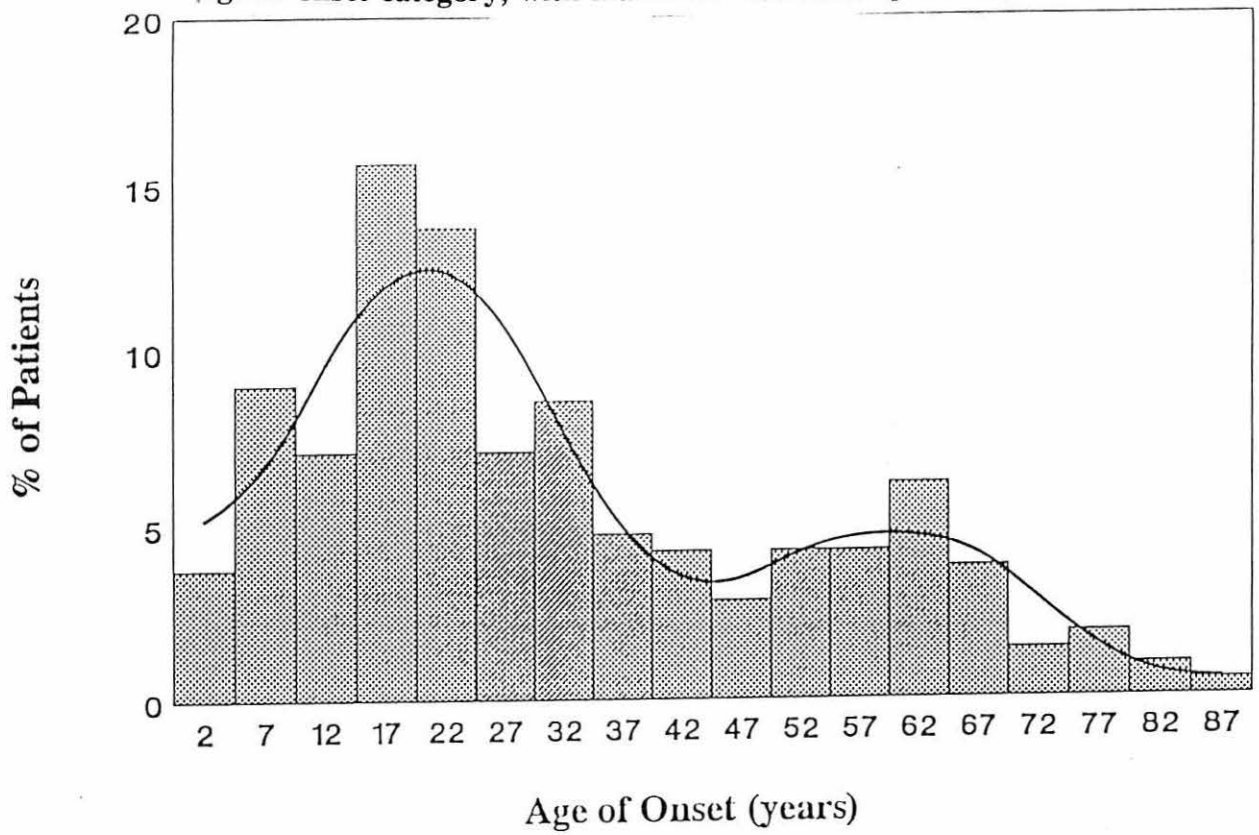
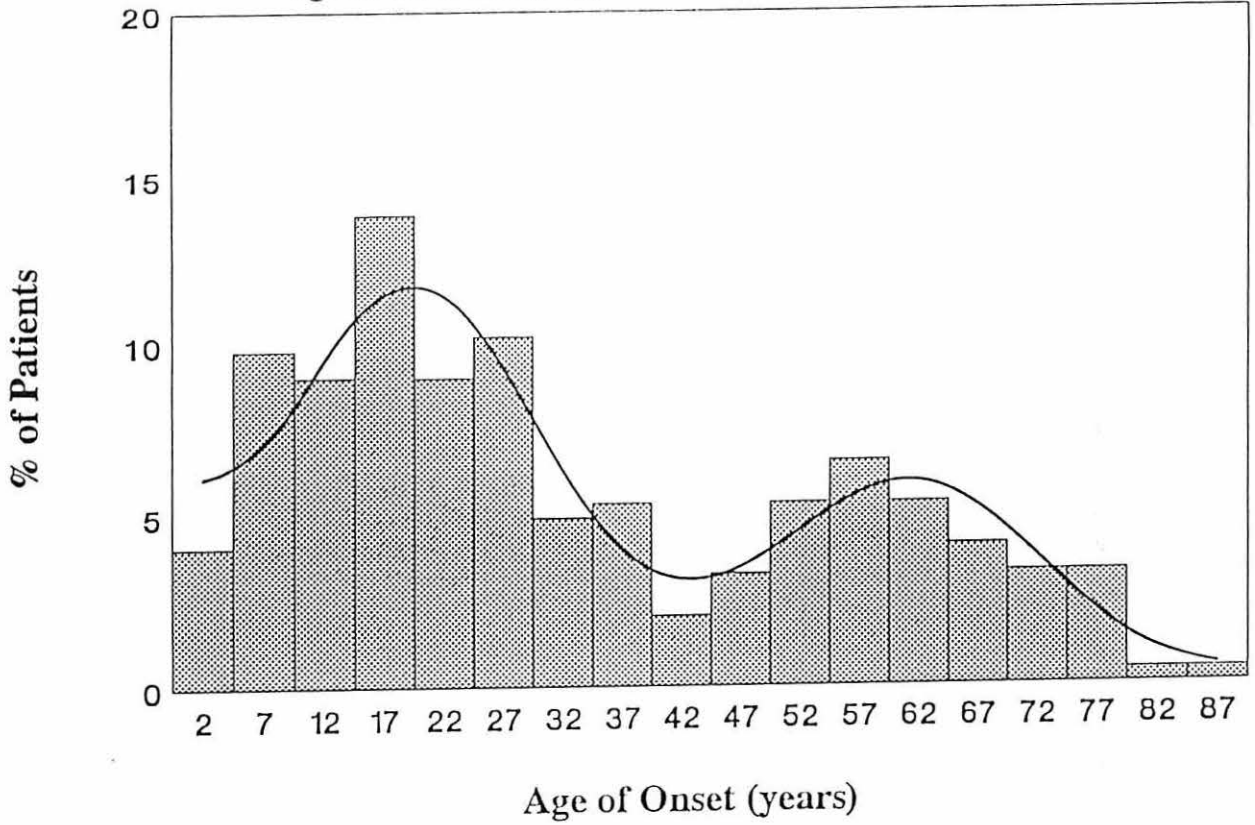


FIGURE 4

Histogram of percentage of female psoriasis patients in each age of onset category, with maximum likelihood plots superimposed



4.4 **Results: age of patients at time of study**

Given the result of the mixture of two distributions in the age of onset of the patients and because questions arose about a possible bias in the ages of the patients, which may influence the onset distribution, it was decided to look at the ages of the patients at the time of study to see if a similar pattern emerged. Results are presented in Table 7 (p110).

Overall the difference in the mean of the age of onset and the age of the patient was 9 years (Table 1, p97). The mean age of all 211 male patients was 40.3 years while the mean age for all 245 female patients was 41.7 years. The range of ages was 1-87 for males and 1-89 for females (Table 7). The medians and means were similar, as were the standard deviations. The calculated skewness in the data for ages for males was 0.16 and for females it was 0.21. In view of this, it was decided to formally test the ages by the method of maximum likelihood for a mixture of distributions.

The ages of all patients at the time of study are given as a histogram in Figure 5 (p111).

4.4.1 Formal Analysis of Age at Time of Study by the Method of Maximum Likelihood

The method of maximum likelihood was applied to all male data of ages at time of study and separately to all female data of ages. A univariate normal model and Models A, B and C of the double normal were used. A univariate normal model was rejected at $p = 0.05$, except for Kent male and female data, but low numbers in the Kent sample make this unreliable.

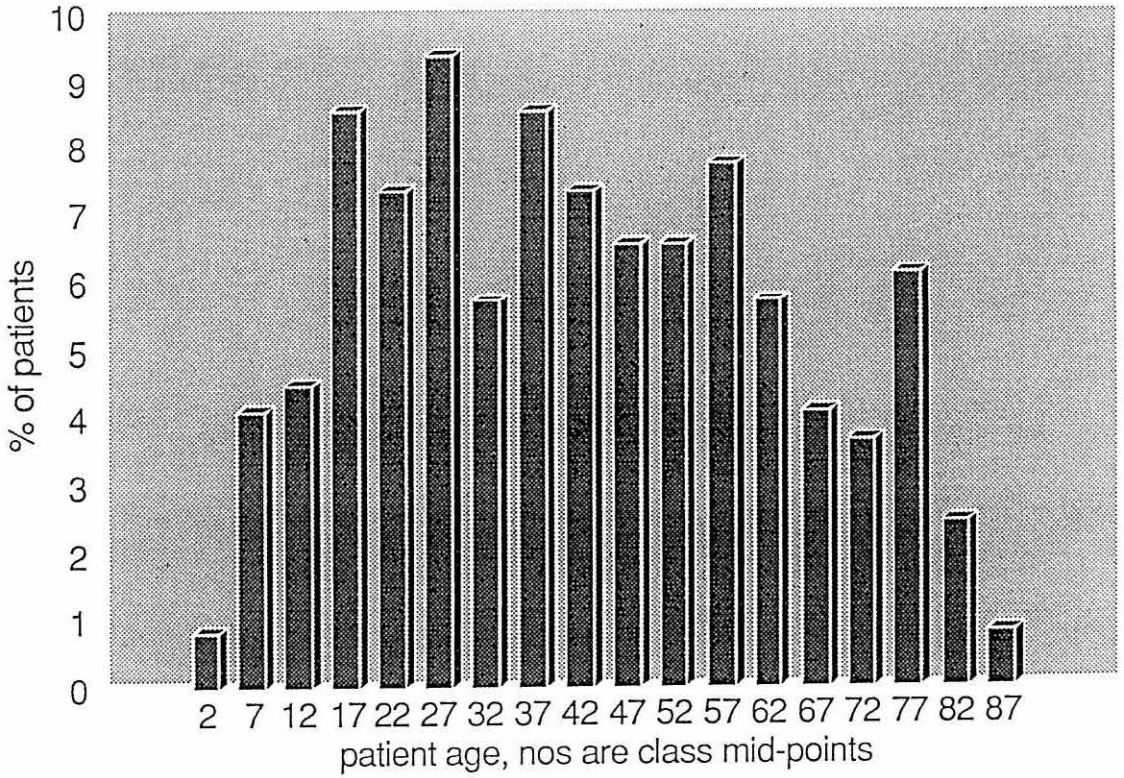
TABLE 7

Basic statistics of ages of psoriasis patients

	n	Mean	Median	SD	Skewness	Range	Lower quartile	Upper quartile
Gwynedd males	158	41.0	41.0	20.6	0.15	1 - 87	23.0	57.3
Gwynedd females	170	41.9	41.6	21.0	0.22	1 - 89	24.8	57.0
Kent males	53	40.6	38.0	18.3	0.16	3 - 77	27.0	51.5
Kent females	75	41.6	40.0	21.8	0.20	3 - 84	23.0	62.0
All males	211	40.3	40.0	20.2	0.16	1 - 87	23.8	54.0
All females	245	41.7	39.0	21.7	0.21	1 - 89	23.8	58.0

FIGURE 5

Histogram of the ages of psoriasis patients at time of examination



Results of the application of the 3 parameter model, Model A, are given in Table 8. This fit of the model to the data was significantly different for the Gwynedd female data ($p < 0.01$) while the model was not significantly different from the data for all other groups ($p > 0.05$). When Model A was applied to the Gwynedd male data a good fit was found ($p = 0.12$); while the application of this model to the Kent male data was also a good fit ($p = 0.81$); as was the fit for Kent female data ($p = 0.63$). There was a good fit of this model to all male data ($p = 0.11$) and to all female data ($p = 0.12$).

Although this model fitted the data well, apart from that for Gwynedd females, this fit was subsequently found to be a poorer fit than that of the other double normal models applied to Gwynedd males, Kent males and Kent females and also for all female data combined. The fit of this model to all male data was the same as that for Model B ($p = 0.11$, Table 10, p115).

TABLE 8

Maximum likelihood fits of ages of psoriasis patients, for males and females and Gwynedd and Kent data and all data combined (3 parameter model)

Patient group	χ^2	**d.f.**	**p=**
Gwynedd males	17.80	12	0.12
Gwynedd females	26.59	12	<0.01
Kent males	7.74	12	0.81
Kent females	9.80	12	0.63
All males	18.17	12	0.11
All females	18.00	12	0.12

The results of the application of the two double normal models, the 5 parameter model, Model C, and the 4 parameter model, Model B, are presented in full in Table 9 (p114) and Table 10 (p115) respectively. Added to these are the calculated 95% confidence intervals (CI).

Best fits overall as suggested by MLP were the 5-parameter double normal model, Model C (Table 9) with unequal variances and unequal proportions), but these gave a fit that was only marginally better than for the 4 parameter model, Model B (Table 10). Fits for all males (Model C) were $\chi^2 = 14.11$ with 10 d.f., $p = 0.17$ compared with $\chi^2 = 16.81$ with 11 d.f., $p = 0.11$ for Model B. Fits for all females (Model C) were $\chi^2 = 8.05$ with 10 d.f., $p = 0.62$ compared with $\chi^2 = 14.03$ with 11 d.f., $p = 0.23$ for Model B. However, Model C estimated means for the overall male age data of 19 years for the younger age group and 47 years for the older age group. Similarly, for female age data the estimated ages were 20 years and 51 years. The younger age means were the same as the early ages of onset means (Tables 5 and 6, p105 & p106) when the overall basic data showed that on average the age at time of the study was 9 years greater on average than the onset. The estimated mean ages for both males and females in the older age group were younger than the means of the ages of onset, but some of the early onset is mixed in with this (ratio 3:2, younger / older ages compared with 2:1 early / late onsets). Model B gave results which were consistent with the basic analysis of the Data (Table 1, p97), and seemed the more appropriate model.

TABLE 9

Maximum likelihood fits of ages of psoriasis patients, for males and females and for Gwynedd (G) and Kent (K) data and for all data combined (5 Parameter Model)

	Younger age					Older age							
	n_1	Propor -tion p	M_1	S_1	95% CI	n_2	Propor -tion p	M_2	S_2	95% CI	χ^2	df	p-value
Males (G)	51	0.32	19.7	8.2	4 - 36	107	0.68	51.5	16.8	19 - 84	13.52	10	0.20
Females (G)	42	0.25	20.2	7.9	5 - 36	128	0.75	50.4	19.8	12 - 89	18.32	10	0.05
Males (K)	46	0.87	36.3	14.9	7 - 65	7	0.13	71.3	5.7	60 - 83	4.48	10	0.92
Females (K)	49	0.66	29.0	13.7	2 - 56	26	0.34	68.0	10.8	44 - 89	7.53	10	0.68
All males	44	0.21	19.7	7.5	5 - 34	167	0.79	47.1	18.9	10 - 84	14.11	10	0.17
All females	71	0.29	20.8	8.7	4 - 38	174	0.71	51.5	20.0	12 - 91	8.05	10	0.62

TABLE 10

Maximum likelihood fits of ages of psoriasis patients for males and females and for Gwynedd (G) and Kent (K) data and all data combined (4 Parameter Model)

	Younger age					Older age							
	n_1	Propor -tion p	M_1	S_1	95% CI	n_2	Propor -tion p	M_2	S_2	95% CI	χ^2	df	p-value
Males (G)	84	0.53	26.0	12.7	1 - 51	74	0.47	58.7	12.7	34 - 84	17.58	11	0.09
Females (G)	105	0.62	29.9	14.4	2 - 58	65	0.38	63.0	14.4	35 - 91	24.38	11	0.01
Males (K)	40	0.76	34.0	13.7	7 - 61	13	0.24	63.9	13.7	37 - 91	6.17	11	0.86
Females (K)	46	0.61	27.6	12.9	2 - 53	29	0.39	65.9	12.9	41 - 91	7.61	11	0.75
All males	122	0.58	28.5	13.4	2 - 55	89	0.42	59.1	13.4	33 - 85	16.81	11	0.11
All females	149	0.61	28.8	13.8	2 - 56	96	0.39	63.7	13.8	37 - 91	14.03	11	0.23

The results of applying the 4 parameter double normal model (Model B), with equal variances, gave the proportions of early to late age distributions as approximately 3:2, which indicates a higher proportion in the older ages than was found for the onsets. This gives an estimated mean of the ages at time of study that was slightly over 9 years greater than the mean of the onset for the early distribution, for both males and females. The estimated mean of the older age distribution was approximately 3 years greater than the later onset mean for both sexes.

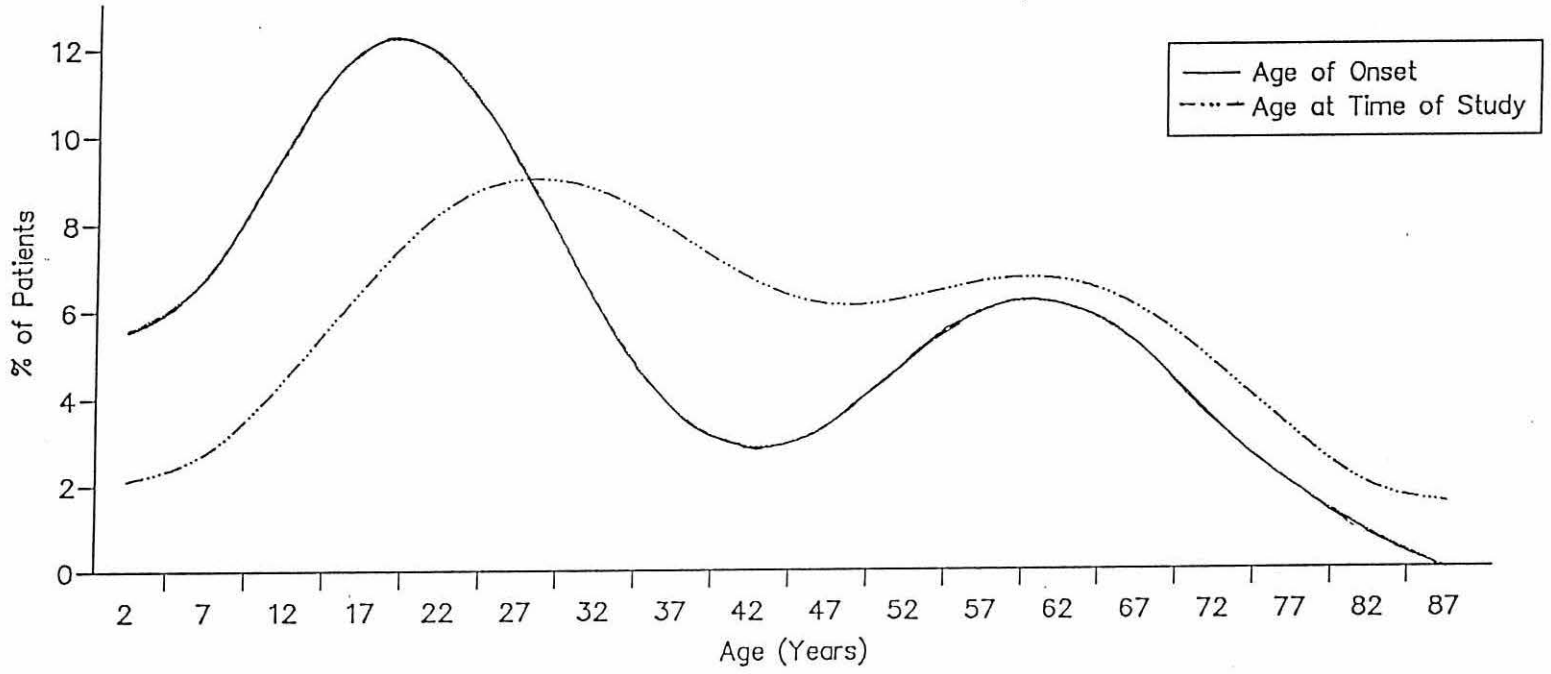
Also, the variances S^2 are greater (S is estimated as 13.4 for males, and 13.8 for females) than for the onset distributions. The confidence intervals show a far greater overlap for the two normal distributions of ages compared with onset distributions (22 years for males, 19 years for females). This is also illustrated in Figure 6 (p117), which is a plot of the ages and the ages of onset of all female patients. The plot for male patients is very similar, but with the application of the method of maximum likelihood indicating a slightly worse fit.

4.5 **Expected ages in the population**

The ages of the patients referred to the clinic did not represent the ages of those patients with psoriasis in the general population, where this includes anybody who has been diagnosed as having psoriasis at any time, not just the current clinical status. Several epidemiological studies on psoriasis have given some statistics on the ages of psoriasis patients in a population, but few have included a distribution of this. No distribution of ages of psoriasis patients in the U.K. from an epidemiological study could be found in the literature. Farber and Nall (1974) however, presented a histogram of ages in 10 year increments, and a comparison with this was sought. If the ages of onset of this present study's data were accumulated to give a profile of ages of those who have ever had an onset of psoriasis, it would be expected that there

FIGURE 6

Fitted maximum likelihood plots of ages and ages of onset for all female psoriasis patients



would be a cumulative distribution curve, reflecting the early and late onset, but not falling off until mortality rates start to have a significant effect in older age.

4.5.1 The Cumulative Onset Distribution and Survival Rates

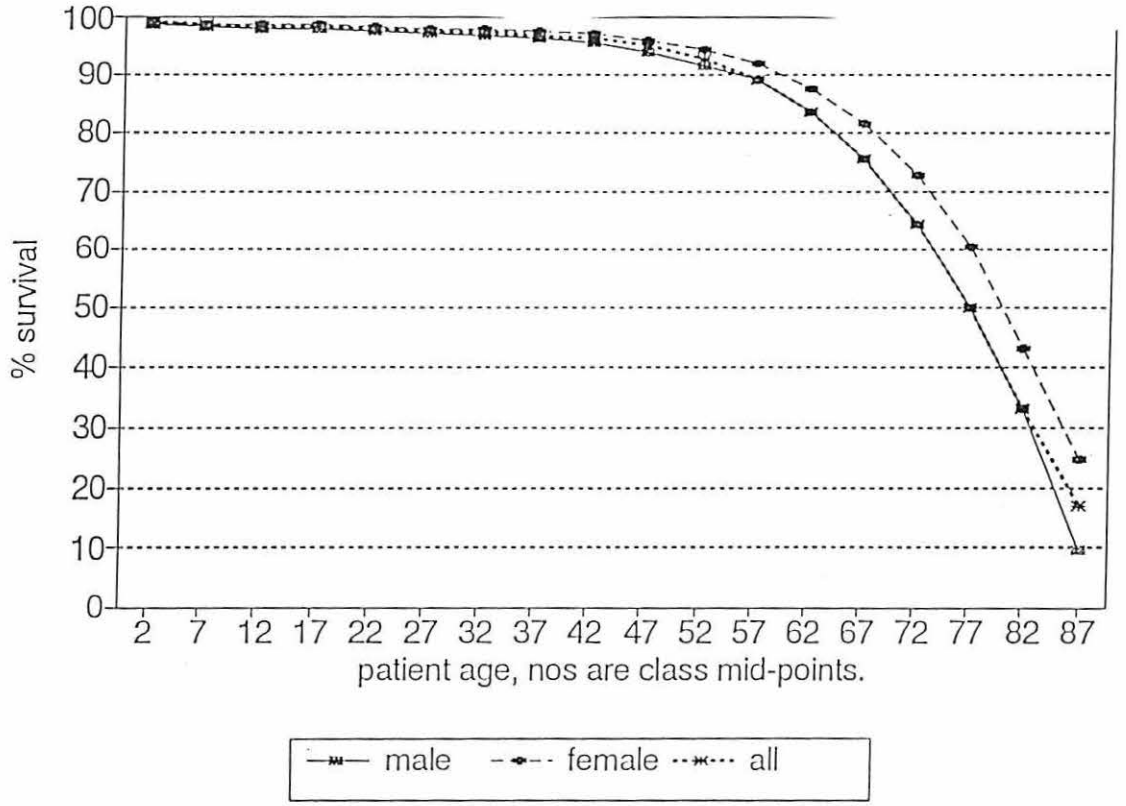
All male and all female onsets of psoriasis in this study were taken as cumulative frequencies in 5 year increments. These frequencies were corrected from birth for survival rates using H.M.S.O. England and Wales Life Tables, (1987) and the number of survivors in each age category of 100 live births of the same sex. The annual survival rates (l_x) were merged into 5 year intervals to match the onset categories in this study (Figure 7, p119). The calculation was carried out as follows:- The survival rate at birth is 100%, while the survival rate between 3-4 years is 98.56% for males and 98.87% for females. Averaging these gave survival rates of 98.9% for males for the ages 0-4 years and 99.2% for females for the ages 0-4 years. The results of taking these percentages of the total frequency whose onset was in the range 0-4 years, inclusive, were taken to be the corrected cumulative frequency of onset. The same process was applied to each 5 year interval of frequencies of onsets, up to the age of 89 years. For example, the survival rate at 85-89 years inclusive averages at 9.92% for males and 24.6% for females.

4.5.2 Formula for Calculating Corrected Cumulative Onset Frequencies

A formula to apply to each 5 year onset category to correct for the survival rates of previous 5 year onset, plus the survival rate of the current onset, was developed by the author. It is an iterative process for estimating the expected cumulative numbers of psoriasis patients over all ages, in the population.

FIGURE 7

Survival rates per age category for males and females and both sexes together, England and Wales data



The author corrected for numbers left after the previous survival number has been applied, for example :-

$$\theta_1 = \frac{\beta_1}{\beta_0}\theta_0 + \gamma_1$$

where β_0, β_1 .. are the survival rates per 100 live births, and θ_0, θ_1 .. are the expected accumulated numbers in each age of onset category, where this equals:-

[(Current survival rate / previous survival rate) x Previous nos who have developed psoriasis] + nos in current age category who have developed psoriasis.

γ_1, γ_2 .. are remaining numbers in each 5 year onset category, from the original 100. $\theta_1 = \gamma_1$ because θ_0 is zero.

In general, this is in the form of:-

$$\theta_n = (\frac{\beta_n}{\beta_{n-1}})\theta_{n-1} + \gamma_n$$

and :-

$$\theta_{n-1} = (\frac{\beta_{n-1}}{\beta_{n-2}})\theta_{n-2} + \gamma_{n-1}$$

Substitute for θ_{n-1} :-

$$\theta_n = \frac{\beta_n}{\beta_{n-1}}\left[(\frac{\beta_{n-1}}{\beta_{n-2}})\theta_{n-2} + \gamma_{n-1}\right] + \gamma_n$$

$$\theta_n = \frac{\beta_n}{\beta_{n-2}}(\theta_{n-2}) + \frac{\beta_n}{\beta_{n-1}}(\gamma_{n-1}) + \gamma_n$$

Similarly substitute for θ_{n-2} , where this is

$$\theta_{n-2} = \frac{\beta_{n-2}}{\beta_{n-3}}(\theta_{n-3}) + \gamma_{n-2}$$

$$\theta_n = \frac{\beta_n}{\beta_{n-2}}\left[(\frac{\beta_{n-2}}{\beta_{n-3}})\theta_{n-3} + \gamma_{n-2}\right] + (\frac{\beta_n}{\beta_{n-1}})\gamma_{n-1} + \gamma_n$$

$$\theta_n = \beta_n\left[(\frac{\theta_{n-3}}{\beta_{n-3}}) + (\frac{\gamma_{n-2}}{\beta_{n-2}}) + (\frac{\gamma_{n-1}}{\beta_{n-1}})\right] + \gamma_n$$

Continue substituting for θ_{n-p} in this way to get :-

$$\theta_n = \beta_n\left[\sum_{k=1}^{k=n}\frac{\gamma_{k-1}}{\beta_{k-1}}\right] + \gamma_n$$

This function gives the expected accumulated numbers of psoriasis patients in each age group. This allows independent calculation of expected percentages of psoriasis patients at any age in the population.

4.5.3 Plots of Corrected Cumulative Ages

Using the above formula, corrected accumulative expected ages were plotted for all males, females and all patients. The resultant plot (Figure 8, p122) initially rises, reflecting the onset distribution, with a flattening of the slope at the age of 40 years and showing a maximum at about the age of 62 years, after which mortalities become dominant. The overall corrected cumulative expected ages for all patients were then compared with the actual ages at examination for all patients (Figure 9, p123). This was carried out to answer questions on whether the ages of the patients were representative of the ages in the population. This will be discussed further in section 4.7.3.

FIGURE 8

Corrected cumulative ages of psoriasis patients, male , female and both sexes

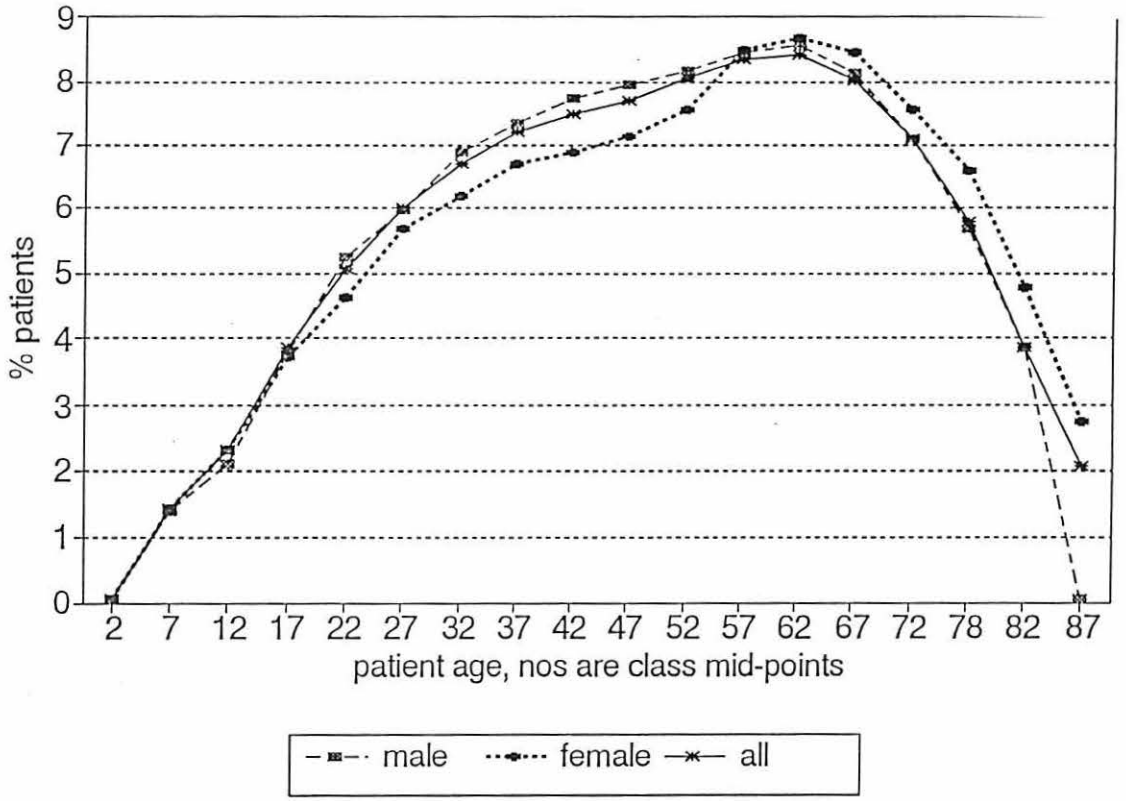
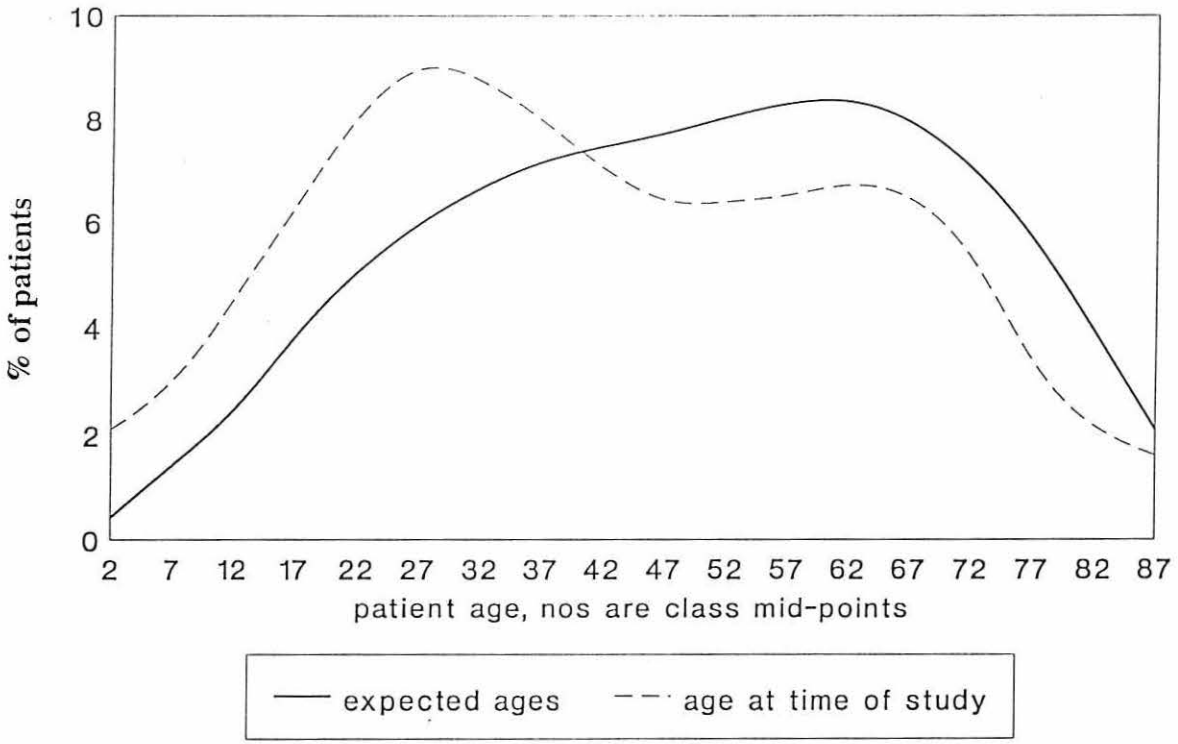


FIGURE 9

Maximum likelihood plots for comparison between the expected ages of psoriasis patients in the population and the ages of psoriasis patients at time of study



4.5.4 Comparison of Expected Ages with Observed Ages in a Population

Farber and Nall's (1974) study, gave data of the ages of psoriasis patients divided up into males and females, both in ten year intervals. A histogram of all ages of onset of this present study compared with all ages of onset in Farber and Nall's data, as a percentage frequency of the total in 10 year increments is presented in Figure 10 (p125). The expected ages in this present study gave a poor fit to the U.S.A. data for male ages of $\chi^2 = 15.87$ with 8 d.f., $p = 0.04$. Similarly, the data for all female ages gave a poor fit to the U.S.A. data of $\chi^2 = 18.43$ with 8 d.f., $p = 0.02$. This iterative process gave greater numbers in the older age categories, but, if the data was examined within the cut-off age of 70 years, the differences were not significant. Males - $\chi^2 = 5.56$ with 6 d.f., $p = 0.47$ and for females - $\chi^2 = 3.55$ with 6 d.f., $p = 0.74$. However, different populations and methodologies were being used. This will be discussed further in section 4.7.3.

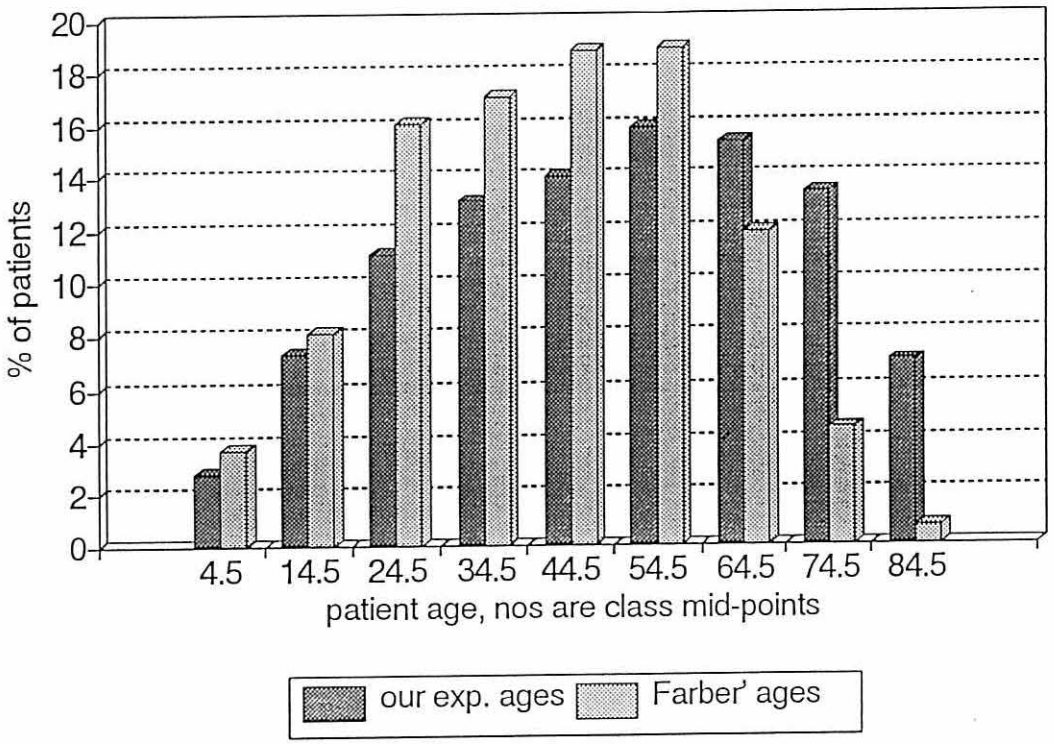
4.5.5 Formal Analysis of Expected Ages and Observed Ages

The method of maximum likelihood was applied to the expected ages in the population for both males and females and for both sexes combined, in the present study. No fit that was not significantly different from a recognised standard distribution could be found for any of these, whether as a mixture of two distributions, or as a univariate distribution. Using the Model C, with unequal variances and unequal proportions, gave results that were significantly different from the data, while the other models gave poorer results. The result for males was $\chi^2 = 18.37$ with 4 d.f., $p < 0.01$ and the result for females was $\chi^2 = 37.62$ with 4 d.f., $p < 0.001$.

MLP was applied to Farber and Nall's (1974) data, a single normal distribution was strongly rejected for both males and females; the fit for males was $\chi^2 = 41.06$ with 7 d.f., $p < 0.001$; the fit for females was $\chi^2 = 93.29$ with 7 d.f., $p < 0.001$. Best fits were found for a double normal model C, with unequal variances and unequal proportions; the fit for males was $\chi^2 = 5.73$ with 4 d.f., $p = 0.22$; the fit for females was $\chi^2 = 8.11$ with 4 d.f., $p = 0.09$.

FIGURE 10

Histogram of ages for comparison with Farber's data of psoriasis patients in the population



(Note:- No model fitted the ages of onset of Farber and Nall's data.)

4.6 Results of affected relatives associated with each age of onset of patients.

4.6.1 Other Studies

Most studies which have dealt with the affected relatives of psoriasis patients gave a percentage of all patients who have a family history of psoriasis. Sometimes this had been presented as a single figure of the number of psoriasis patients who had at least one first degree relative with the condition, regardless of age of onset. In other instances, an approximate age of onset in the patients were considered, for example, Henseler and Christophers (1985) stated that more then half the patients with psoriasis of early onset had affected first degree members, while affected first degree relatives were virtually absent in the late onset patients. This conclusion was drawn from taking two windows of onset (15-25 years) and (60-70 years) and asking patients whether they had a father, mother or sibling affected. They found that they recorded 27 fathers, 17 mothers and 14 siblings for the early onset window and only a total of 2 siblings for the late onset window.

4.6.2 A Comparison with Other Studies

All 328 Gwynedd psoriasis patients whose age of onset could be ascertained were used in this section of the study. The familial data for the retrospective Kent sample were not available . In the data, the relatives were undivided by sex and so it was decided to examine the relatives of male and female patients combined, also this increased numbers in the onset categories. Results are presented in Table 11 (p127).

The subgroup of patients (328) who had an exact age of onset recorded was tested against the original data of 428 patients, in respect of numbers of relatives. Of the subgroup, 166 relatives had psoriasis out of a total of 1774

TABLE 11

Relationship of onset of psoriasis in patients to familial psoriasis, with correction factors applied for the increasing number of relatives accumulated with increasing age in the patients

Age of onset (years)		Correction factors	% patients with at least one relative with psoriasis	
			Uncorrected	Corrected for age
<40		1.23	43.6	53.5
	<10	1.35	57.5	77.6
	10 - 19	1.26	47.5	59.9
	20 - 39	1.14	38.9	44.3
≥ 40		0.80	21.4	17.1
All ages		1.02	34.6	35.3

(9.36%), while 243 of the relatives in the original data, out of a total of 2488 (9.79%) had psoriasis. These results are not significantly different ($p = 0.64$).

Those with at least one first degree relative with the condition, are presented in Table 11, column 4 (p127). The format was chosen to compare this study's results with those of other studies. The onsets were divided into early and late onsets at the age of 40 years, in accordance with the results of section 4.3. The lower onset was subdivided to see if onset at a young age indicated a greater familial psoriasis incidence.

These results gave a preliminary idea that the patients with earlier onset have a greater familial association for psoriasis. However, as the patient gets older, more relatives would have been accumulated, and the relatives themselves will also be getting older and will have an increasing cumulative incidence of psoriasis in them. The mean number of relatives with or without psoriasis was 5.41 . Using this as a weighting factor and standardising all the results in column 4 of Table 11 (p127), produced the corrected number of first degree relatives in column 5, and this demonstrates an enhancement of the earlier onsets having a greater percentage of familial psoriasis. Correction factors involved are given in column 3 of Table 11 (p127), after standardisation using the mean number of relatives.

4.6.3 The Approach of the Present Study

No other study had looked in detail at the distribution of the number of affected relatives associated with the age of onset of patients. This part of the study aimed to do this by examining the frequency of affected relatives and also the unaffected relatives in 5 year patient onset categories to equate with the results of the age of onset distributions, and to discern any emergent pattern. Ideally the ages of onset of the affected relatives could have supported, or otherwise, the onset distributions. The sample data, however, did not contain this information, so a simple approach was decided upon.

Initially, the total number of all affected relatives of patients in each onset category were analysed in 5 year increments. It was realised that these did not reflect the total number of relatives whether affected or not. Moreover, it did not take account of the difference of approximately 9 years between the age of onset and the age of the patient at the time of study (Table 1, p97).

4.6.3.1 Development of age of onset / age correction model

It was decided that if this difference between the onset and the age at the time of examination were to be accounted for, all patients would have to be placed into some form of age and age of onset categories. The more crude the category, the greater the numbers and the greater the accuracy of estimation. However, for comparison with the onset distributions (section 4.3) it was decided to have "cells" with an axis of 5 year increments for onsets and 5 years increment for ages. A table framework was devised for this. When the data was applied to this, it produced for all ages of onsets and ages a table with total relatives in each category and similarly a separate table with the number of affected relatives in each category. Combined, this resulted in a percentage in each "cell" or category of affected relatives for that age of onset / age (Table 12, p130). Some categories had zero percentages, meaning that no relatives were affected while others were blank, indicating that no patient fell into that category. Tabling age of onset to age in this way showed the automatic correction for any differences in the number of relatives as the patient gets older, in comparison with the onset, and also for increasing prevalence of psoriasis within these relatives as they have increasing time in which to manifest the condition.

A total percentage for all the cells of the age of onset categories was then divided up by the number of cells to give a mean or average percentage per age of onset (right hand column, Table 12). This indicated a minimum

TABLE 12

Table of the percentage of affected relatives in each category of age of onset to age of psoriasis patient

Patients Age of Onset (years)	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-89	Relatives Total %	Relatives Avg. %
70-89															2.4	2.4	2.4
65-69														0	0	0	0
60-64													3	0	7.4	10.4	3.5
55-59												3.4	15		7.7	26.1	8.7
50-54											4.5	8.3	16.7	8.3	20	57.8	11.6
45-49										8.8	5.6	0				14.4	4.8
40-44									3.7		0	7.7	16.7		11.1	39.2	7.8
35-39								5.3	11.1	0	3.6	3.0		0		23	3.8
30-34							9.7	0	25	4.8	0	0	0	0	0	39.5	4.4
25-29						13.6	0	0	17.6	0	0	33.3	0			64.5	8.1
20-24					15	17.8	23.0	16.7		30	6.2	0				108.7	15.5
15-19				7.5	12.1	10.3	0	20	11.4		12.5		3.8		0	77.6	8.6
10-14			12.1	8	15.4	18.2	42.9	0				60			0	156.6	19.6
5-9		11.3	0	13.8	16.7	29.6	0	7.1		0	35.7		50		50	214.2	19.5
0-4	25	0	14.3	0			26.7									66	13.2

Age of Patient (years)

between earlier and older age of onset, with respect to relatives with psoriasis, at the class with mid-point of 37 years.

4.6.4 Formal Analysis of Distribution of Number of Relatives by the Method of Maximum Likelihood

The data here is discrete so several discrete distributions were applied, using the method of maximum likelihood. Since no models are available for this in MLP in the form of a mixture of two distributions, and no single discrete distribution overall fitted the data, the data was split up at the age of onset of 40 years and the earlier onset data tested separately from the late onset data.

A Poisson distribution for early onset was rejected, $\chi^2 = 20.05$ with 7 d.f., $p < 0.01$. Late onset data gave a reasonable fit for a Poisson distribution of $\chi^2 = 11.14$ with 9 d.f., $p = 0.27$, but when the end classes were amalgamated because of low, or zero, frequencies a result of $\chi^2 = 5.86$ with 5 d.f., $p = 0.32$ was found. MLP gave a fit of a negative binomial of $\chi^2 = 5.93$ with 6 d.f., $p = 0.43$ for early onset and $\chi^2 = 4.79$ with 5 d.f., $p = 0.44$ for late onset, when the end classes were amalgamated for low frequencies. The Poisson index of dispersion for early onset was 1.46 and for late onset 1.24, indicating values not very close to 1, where a value of 1 is indicative of a Poisson distribution. The negative binomial index of dispersion calculated form the results was 6.31 for early onset and 3.44 for late onset. These are much greater than 1 and indicate lack of randomness and independence, that is, a contagious distribution, where the data is clustered together.

The best fits therefore were found to be 2 negative binomial distributions, with separation at 40 years, even though a Poisson distribution fitted the data well for late onset. The statistics of maximum likelihood fits of these negative binomials are given in Table 13 (p132).

TABLE 13

Statistics of maximum likelihood fitted negative binomial models for affected relatives associated with age of onset in the patient

Patient group	n	M	Var	k	disp. index	χ^2	d.f.	p-value
<40 onset	222	2.59	4.02	4.69	6.31	5.93	6	0.43
>40 onset	106	2.15	2.72	0.04	3.44	4.79	5	0.44

The negative binomial is an example of a contagious distribution where there is aggregation of data. It arises from research into infectious diseases where the likelihood of an event is more likely if there are other events in the vicinity. The results of maximum likelihood fits in Table 13 demonstrate this aggregation.

Figure 11 (p134) is a histogram of the percentage of relatives who have psoriasis in each patient onset category, when corrected for age of the patients. Superimposed on this are the two maximum likelihood plots, indicating a fit of two negative binomials when the data is separated at 40 years of onset of the patient.

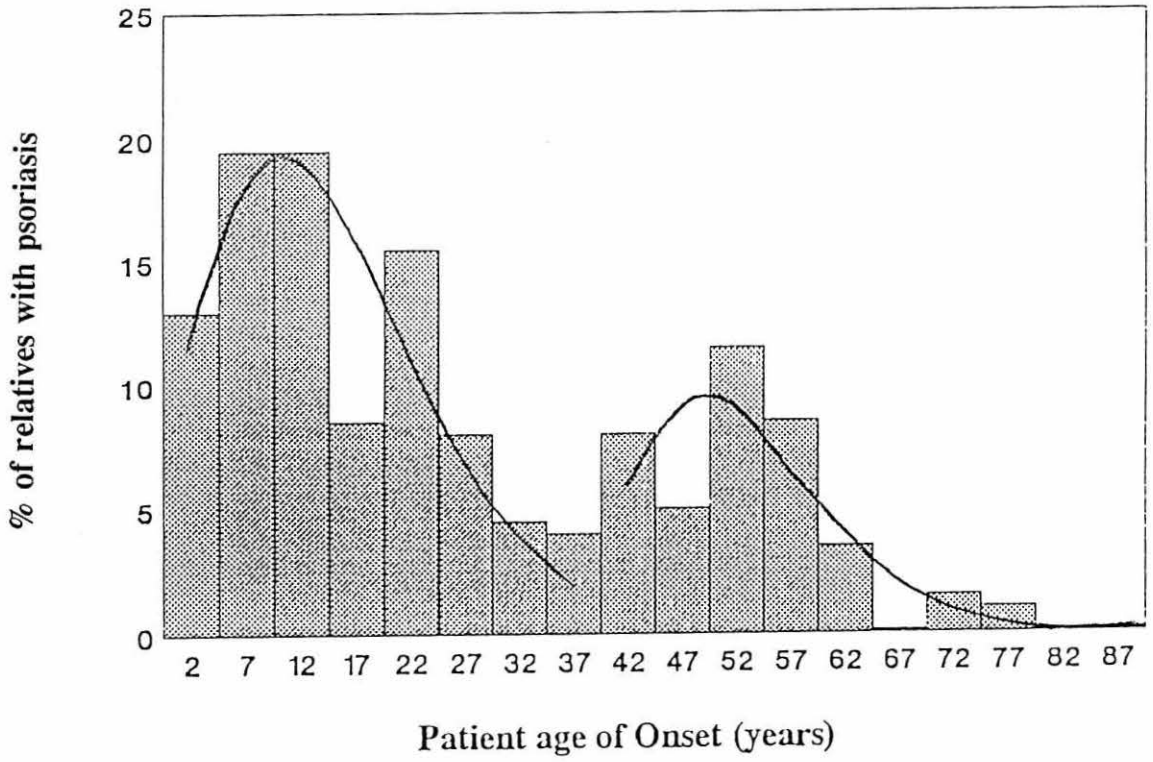
4.6.5 Evaluation of Confounding Factors

Parents and siblings age along with the patients, but there would be many more children of the older age group who would be old enough to manifest psoriasis. For example, those patients in their 40's and 50's could have children in their late teens and 20's which is where the peak of the first onset of psoriasis occurs in the early onset group. This could mean enhancement of numbers of relatives with the condition in the 40's and 50's, that is, where the peak of the second negative binomial occurs when the method of maximum likelihood is applied.

It was thought therefore that the inclusion of children could be a confounding factor in the assessment of familial psoriasis, especially with regard to the later onsets in the patients. The presence of children with psoriasis was tabled in the same way as all relatives and the results subtracted from total numbers in each category of age of onset / age. This resulted in a distribution that was not significantly different from that of all the relatives (χ^2 = 10.41 with 14 d.f., p = 0.73). Thus the possibility of the children contributing significantly to the late onset results was excluded.

FIGURE 11

Percentage of affected relatives associated with age of onset in psoriasis (maximum likelihood plots are superimposed)



4.7 **Differences in features between early and late onsets**

An examination of the clinical features of psoriasis (section 3.2.2) found to be significantly different from controls was carried out, in respect to the two age of onset distributions in order to detect whether there was any factors distinguishing the two. A table of these was drawn up (Table 14, p136). Results, generally, for the group with late onset, indicate a reduced prevalence of these features, compared with those of early onset, some significantly, such as affected area itching, scaling in the ears, seasonal changes and retro-infra auricular intertrigo. This fits in well with many other studies which suggest that the younger the age of onset, the more serious the disease process. These results are not in conflict with the hypothesis that there may be two genotypes involved in psoriasis, but they appear to be manifested in much the same phenotype.

4.8 **Discussion**

4.8.1 Age of Onset

Previous epidemiological studies (for example, Farber and Nall, 1974) may well have a mixture of distributions in the age of onset data which is obscured by presentation. For example, using a large class interval in a histogram may conceal the real pattern, and without rigorous statistical analysis the mixture cannot be detected and defined. A comparison with this study's data in 10 year increments shows that the two data sets come from different populations, since χ^2 tests show significant differences in the distributions for males ($p < 0.01$) and for females ($p < 0.001$). The onset data of this study has greater percentages of older onsets.

The preliminary analysis (section 4.3.2) indicated that there may well be a mixture of distributions present with histograms indicating overall that there is a minimum at the age of onset 40-44 years. Basic statistics indicated

Table 14

Features of psoriasis patients, significantly different from controls, and the differences between early and late onsets

Feature	Age of onset of psoriasis					
	< 40 years n(%)	≥ 40 years n(%)	p - value	All psoriasis n(%)	Controls n(%)	p - value
Affected area itch	119 (58.7)	40 (44.6)	< 0.05	194 (45.3)	10 (3.5)	< 0.001
Scaling in ears	105 (51.2)	28 (30.7)	< 0.001	192 (44.9)	11 (3.9)	< 0.001
Dandruff	95 (46.3)	38 (42.2)	= 0.256	187 (43.7)	28 (9.9)	< 0.001
Seasonal change	85 (41.5)	15 (16.7)	< 0.001	155 (36.3)	3 (1.0)	< 0.001
Auricular intertrigo	91 (44.4)	24 (27.0)	< 0.001	154 (35.9)	6 (2.1)	< 0.001
Lichenification	41 (20.0)	19 (21.1)	= 0.415	88 (20.5)	2 (0.8)	< 0.001
Severe/night itch	11 (5.6)	9 (9.6)	= 0.126	38 (8.8)	2 (0.8)	< 0.001
Seborrhoeic dermatitis	17 (8.3)	6 (6.7)	= 0.312	31 (7.3)	7 (2.5)	< 0.001
Nummular eczema	3 (1.5)	4 (4.4)	= 0.106	10 (2.3)	5 (1.8)	< 0.01

modes at 21 for males and 16 for females, indicating a typical earlier onset for females, but apart from this, the distributions shown in Table 2 (p101) show no significant differences for males and females. These distributions also appeared to be symmetrical when divided at the age of 40 years into early onset and late onset.

This led to formal analysis of the overall distributions by the method of maximum likelihood. The programme produced the best fits overall as being a double normal distribution with clear division at the age of onset at 40 years for Gwynedd data, Kent data and the combined data. With the exception of Gwynedd males, the 4 parameter model which assessed the early onset and late onset distributions as having equal variances and unequal proportions was the best fit. The model with unequal variances gave marginally the best fit for Gwynedd males, but this does not alter the basic conclusions. The proportion of the early/late onset ratio, being approximately 2:1, could be due to several factors: Mortality rates calculated using the survival tables described in section 4.5.1 show that, below the age of 40, the mortality rates for both males and females are less than 5%. However, averaging the mortality rates in the late onset group of 40-89 years, gives an overall mortality rate for males of 34.4% and for females of 25.1% This means that between a quarter and a third of the lower numbers in the late onset group is accounted for by mortality rates alone. Another factor may be decreased reporting in older age groups where psoriasis would be seen as a non life-threatening condition and milder forms ignored. However, a weaker genetic linkage is also possible.

The finding that both a prospective sample (Gwynedd) and a retrospective sample (Kent) showed the same bimodal distribution pattern is seen as strong evidence for the presence of two types of psoriasis, in relation to age of onset. This is in agreement with Henseler and Christophers (1985).

A similar pattern has been found in onset for diabetes mellitus over a lifetime (Gamble and Taylor, 1969). The proportions are however, reversed,

since in diabetes mellitus Type I of earlier onset has less numbers than Type II of later onset .

4.8.2 Age at Time of Study

When examining the ages of the psoriasis patients at the time of study to see if these showed any sign of influencing the apparent onset pattern, maximum likelihood results were not very convincingly in favour of any particular distributional pattern. In particular, a good fit for all the double normal models was shown when applied to Kent male and female data. Overall, it was the 5 parameter model which gave the best fits, but although the probability of this being the appropriate model for the data was statistically greater, it was rejected because the estimated parameters were inconsistent with the basic data. The basic data analysis showed an age approximately 9 years greater than the age of onset, whereas the model gave means for the later distribution which were lower than the means of onset, which is not possible. This led to the 4 parameter model (Table 10, p115) being adopted as the probable appropriate model, being only marginally less a good fit to the data and being consistent with it. Here the means for all males and for all females are 9 years greater than onset and also the variances are larger than onset variances by 3 years.

The onsets are reflected in the ages of the patients at the clinic and this could be due to several factors. In Britain, general practitioners (G.P.s) mostly refer patients, when they first present at the practice, to a dermatology clinic for diagnosis, assessment and prescription of treatment routine by the "specialist" dermatologist. These patients generally are referred back to the G.P.s practice for the continuing therapy. Some patients who are difficult to treat or are unresponsive to treatment, generally those who have severe psoriasis, keep attending the clinics. This is reflected in the larger means and variances for ages compared with ages of onset, and also the length of delay and its variability between patients in presentation at the clinic after the initial onset. (Any latent period between the actual triggering of psoriasis and the

condition obviously manifesting itself is not included in this. Burch and Rowell (1965) estimated this to be approximately 3 years but also commented that this would have negligible effect on the pattern of distribution of onsets over about the age of 15 years.) Patients with early onset can have a lifetime of attending the dermatology clinic (age range 1-87 years in this study), giving a long interval between the age of onset and the actual age in some of these patients. This distribution tails off due to the patient being referred back to the G.P. for treatment, remission in their condition, or cumulative mortality in the general population. When patients have a late onset of psoriasis, a new set of patients is introduced into the clinic, mixing with the earlier group who are still attending. These patients only have, at most, half a lifetime's presentation at the clinic (age range 41-87 years in this study). This second distribution is subject to all the same delays as before in presentation at the clinic, but is more sharply affected by mortality rates in the general population.

It must be emphasised that this lengthy analysis of the ages only serves as an adjunct to the main result of the two distributions in the onset. The apparent confounding factor which is demonstrated in the distribution of age of the patients, at time of examination, is a function of the two onsets and the pattern of patient referral in Britain, rather than being a cause of the bimodality found in this study.

4.8.3 Expected Ages in the Population

Dermatologists outside Britain might find the results of the ages at the time of study difficult to understand. In other countries, patients would not necessarily go to a G.P. equivalent for referral but go directly to a specialist clinic for treatment at every stage. They would therefore be more like those present in the population in terms of age distribution. It was hoped to convince others of the lack of bias by formulating a way of transforming this study's data to that expected in the population. Ideally, a study of the

population of Gwynedd would be done, but there were insufficient funds or time for this.

The methods outlined in section 4.5 served to make the data comparable with epidemiological studies. Farber and Nall's (1974) study is the only one found in the literature with ages in 10 year intervals, others had referred to crude ages of onsets. Their study consisted of a long self-administered questionnaire which may have precluded those of extreme old age returning the information. This may partially account for the discrepancy between the calculated expected ages in this study and the ages in Farber and Nall's study, but without further information on the methodology this cannot be quantified. Both are presented as a percentage of the total numbers involved and this study demonstrates a shift to older ages (Figure 10). This apart, the similarities below the age of 70 years show that the psoriasis patients in this study appear to come from a population whose ages are comparable with other populations and perhaps other populations have the same onset pattern. It is possible that Farber and Nall's onset data may show bimodality if presented in 5 year, or less, increments.

4.8.4 Affected Relatives

Reporting of the first degree relatives were believed to be accurate in this study. These were largely those who attended the same clinics as the patients and were known to the dermatologist involved, thus avoiding inter-observer variation.

Epidemiological surveys have reported estimates of familial involvement varying from 4.4% of psoriasis patients having a family member with the condition (Gorbulew, 1928) to 90.9% (Lomholt, 1963). Farber and Nall (1974) found that 47% of psoriasis patients had a first degree relative with the condition. Also they found that three quarters of those whose ages of onset were less than 30 years had "familial aggregation". Hellgren, 1967 found that 6.4% of relatives of psoriasis patients were affected. These conflicting results

indicate varying methodologies and the results are not readily comparable with each other.

The results of this study, in terms of psoriasis patients having at least 1 relative with the condition for comparison with other studies (Table 11, p127), are broadly in line with the findings of other researchers. This study reported 35% of psoriasis patients having at least one relative with the condition. This is in agreement with Fry (1988) who stated that "the general consensus is that approximately one third of patients have a positive family history". In particular agreement with others, this study shows that the earlier the age of onset, the greater the familial association.

Since older patients have accumulated more first degree relatives, that is, more siblings and children, it was thought necessary to correct for these accumulated relatives by standardising all the results for prevalences in the family by an upward factor for early onsets and a downward factor for later onsets, based on an average number of relatives per patient (Table 11). This is approximate and does not allow for time-lapse in the possible initiation of the disease. Nevertheless, it gives an idea of the enhancement of the differences in prevalence in the family between earlier onsets and later onsets, when actual numbers of relatives are taken into account.

Addressing the question of the familial association from another perspective, as one where the ratio of relatives who have psoriasis is compared with those who have not, enabled the development of the age / age of onset model (Table 12, p130). This led to calculation of the average percentage of relatives in each age of onset category and the application of the method of maximum likelihood. The results indicated two negative binomial distributions, when separated at 40 years, as the best fits (Figure 11, p134 and Table 13, p132), which was the first indication that familial incidence of psoriasis may support a hypothesis of their being two onset groups for psoriasis. This result is also consistent with accepted theory that the earlier the age of onset, the greater the familial incidence. This holds true for both early and for late onset separately. Overall, the total relatives associated with all the

ages of onset in the patient demonstrates a ratio of affected relatives of early to late onset of 2.5:1 (Table 12, p130) which is also in agreement with that generally accepted. This ratio is independent of the patients' early / late onset ratio of 2:1 since the relatives are presented as a **percentage** of total relatives per onset category. It is possible that sociological factors could affect the ratio in the relatives, for example, those with late onset may be more unaware of relatives having psoriasis, but it is also possibly indicative of a weaker genetic association being involved.

Questions arise about why the two distributions in of the number of affected relatives have an initial rise rather than starting from the maximum. When the histograms are constructed in 10 year intervals, the maximum frequency in the relatives is at the first ten year interval for each onset group. However, when constructed at 5 year intervals, the late onset distribution will have a mixing area with the tail of the first distribution and thereby could account for this initial rise. The author proposes that the initial rise in the early onset distribution may, in part, be due to conflicting diagnoses and reporting, that is, the confusion in infancy between psoriasiform napkin dermatitis, seborrhoeic eczema, atopic dermatitis and other dermatoses. It may also be that "nappy rash", as these may be labelled, could run in families and be forgotten about when questions of psoriasis arise later. A more likely explanation is the effect of the latent period which is known to exist in psoriasis. Rises in the fitted negative binomial distributions are due to the probability density function and the degrees of freedom (1 degree of freedom would produce a function which starts at the maximum and falls off).

Ideally, the ages of onset of psoriasis of all the relatives would be treated in the same manner as the patients' ages of onset in direct comparison for the confirmation of the early and late onset distributions. This data was not available to this study, and such information would involve a very large study of a population, otherwise questioning patients about onsets in relatives would be subject to many inaccuracies.

The findings of this part of the study are in disagreement with other studies. Melski and Stern (1981) gave no evidence of two distributions and treated onset in psoriasis as a single distribution and stated that psoriasis occurrence in relatives was independent of onset. However, their patients were all severe psoriasis cases and this may influence the results. Similarly, Henseler and Christophers (1985), examined records of severe hospitalised patients (section 4.6.1) and concluded that those of early onset appeared to have a familial association and those of late onset appeared to have no familial association. This led to their statement that "psoriasis shows two distinct forms, one of which is hereditary, with early onset, and the other is sporadic and occurs in older age". They labelled the two forms Type I, the "inheritable form with early onset" and Type II, the "non-inheritable type, with late onset". This was subsequently extensively quoted in the literature.

4.9 **Concluding Comments**

The fitted mixture of two normal distributions in the age of onset of psoriasis patients indicates the possibility of two types of psoriasis in this respect. It is possible that the similarity in distributional pattern shown by both early and late onsets is indicative of similar genotypic factors influencing onset, but with a weaker genetic influence in later onset.

Furthermore, the fitted mixture of two negative binomial distributions in the affected relatives, associated with age of onset in the patients, also indicates that here are two types in relation to age of onset. For early and late onsets, separately, there are increased prevalences in the family at the beginning of each distribution, in line with accepted theory that the earlier the onset in the patient, the greater the number of relatives who have psoriasis. This is consistent with even a single distribution overall as had been accepted in the past, since this study's early /late onset ratio in the relatives is 2.5:1 .

The matching of the pattern of these distributions suggest two hereditary types of psoriasis rather than the second onset type being non-hereditary.

APPENDIX

Results of preliminary data analysis, giving Shapiro-Wilks tests and testing for the presence of a mixture of distributions using an adaptation of Foulkes (1979) method. These results led to the formal analysis by the method of maximum likelihood as detailed in the text.

FIGURE A1

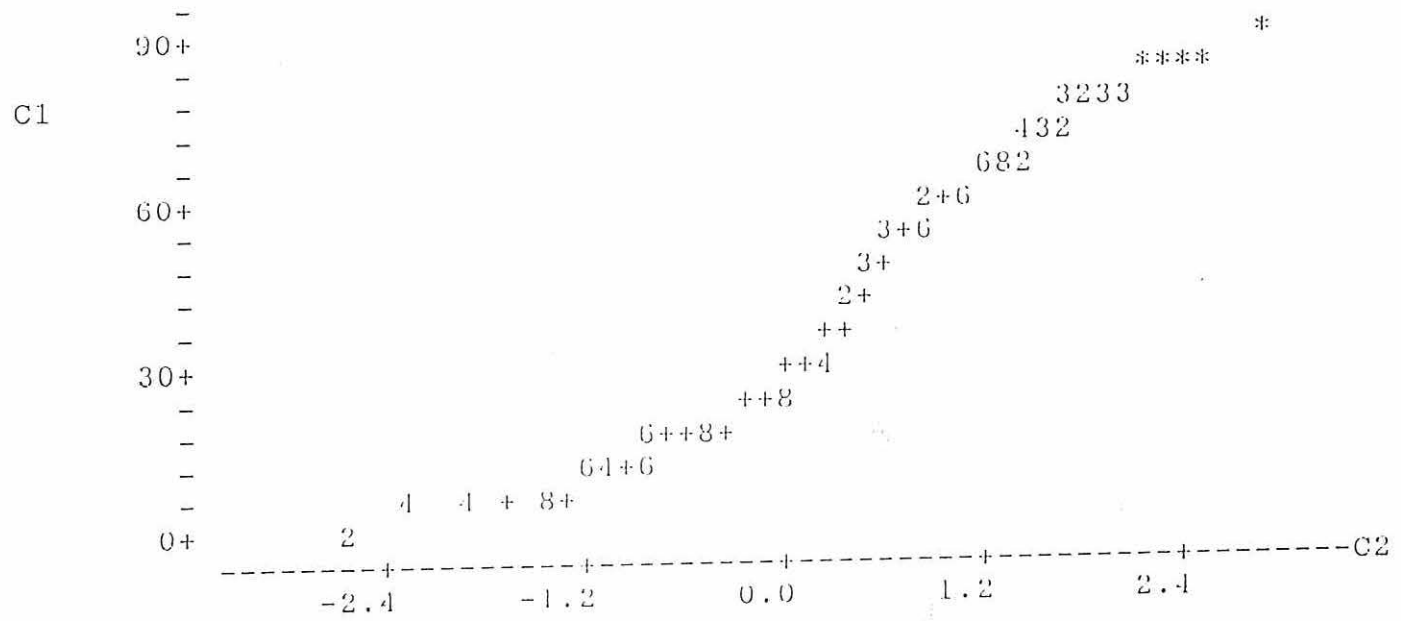
HISTOGRAM OF GWYNEDD ONSET DATA

```
Midpoint    Count
       0       10  ******
      10       58  **********************************
      20       88  ***************************************************:
      30       48  ****************************
      40       24  **************
      50       28  ****************
      60       37  *********************
      70       19  ***********
      80       14  ********
      90        2  *

Histogram of C1    N = 328

Midpoint    Count
    2.00       10  ***********
    7.00       34  ***************************************
   12.00       24  ****************************
   17.00       38  ********************************************
   22.00       50  ************************************************************
   27.00       22  **************************
   32.00       26  ******************************
   37.00       14  ****************
   42.00       10  ***********
   47.00       10  ***********
   52.00       18  *********************
   57.00       18  *********************
   62.00       19  **********************
   67.00       12  **************
   72.00        7  ********
   77.00       11  *************
   82.00        3  ***
   87.00        2  **
```

FIGURE A2

SHAPIRO - WILKS TEST ON GWYNEDD ONSET DATA

```
MTB > nsco c1 c2
MTB > plot c1 c2
```




```
MTB > corr c1 c2

Correlation of C1 and C2 = 0.964

MTB > exec 'pub:nscore'
number of observations (at least 3) :-
The correlation coefficient should be at least k63
to be normally distributed at the 5% significance level.
MTB > print k63
K63       0.996045
MTB >  not normally distributed
```

FIGURE A3

FOULKES METHOD - GWYNEDD ONSET DATA

```
MTB > sort c1 c3
MTB > set c4
DATA> 1:328
DATA> end
MTB > let c5=(c4-1/2)/328
MTB > let c6=(c3-mean(c3))/stdev(c3)
MTB > cdf c6 c7;
SUBC> normal x s.
MTB > let c8=c7-c5
MTB > plot c8 c6
```

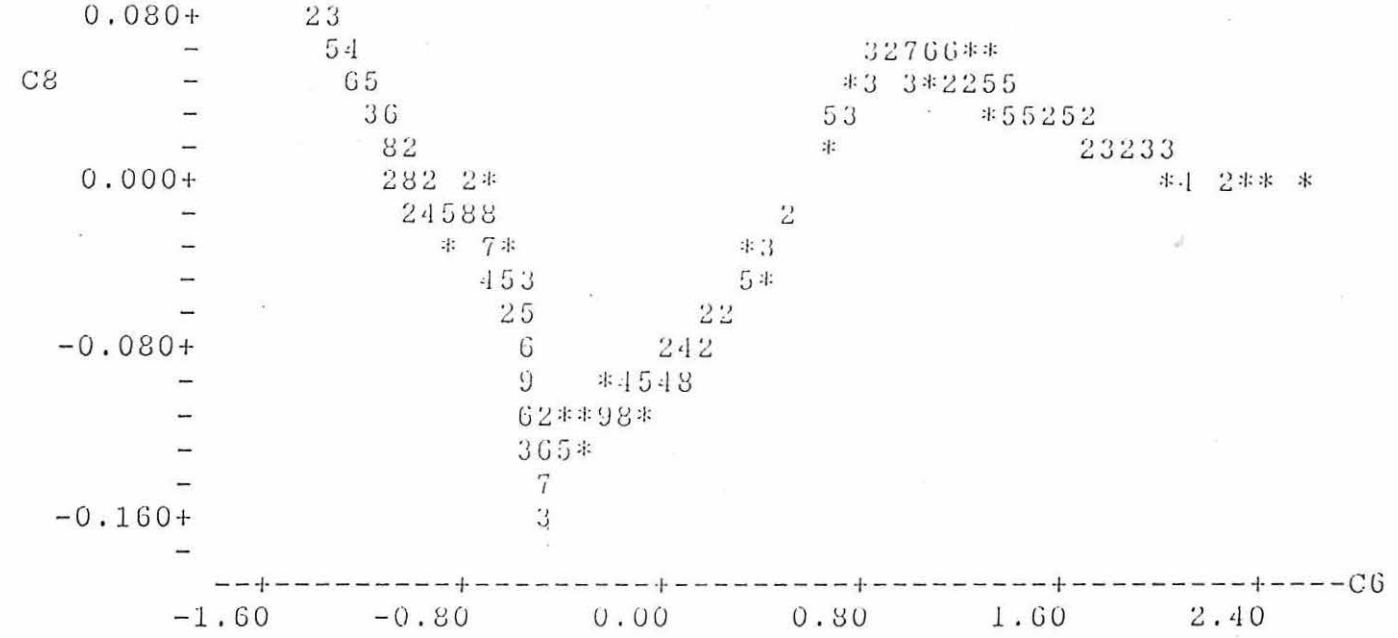


FIGURE A4

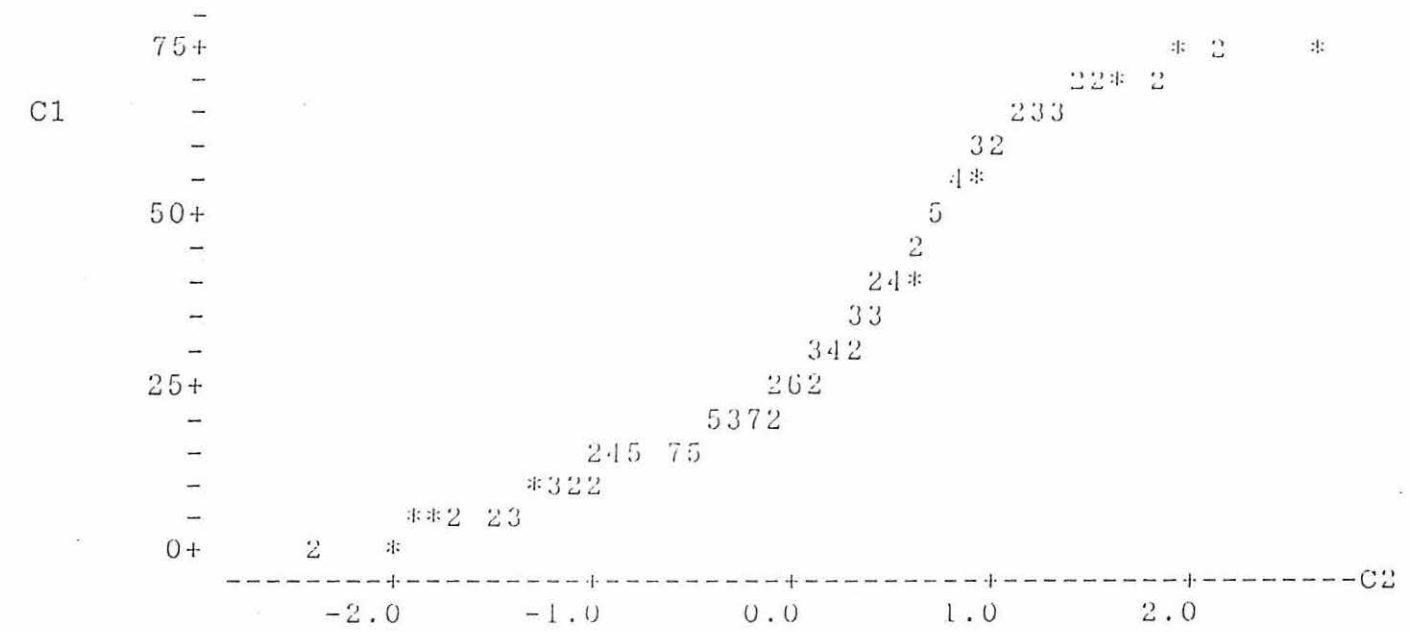
HISTOGRAMS OF KENT ONSET DATA

```
Midpoint    Count
       0        5  *****
      10       21  *********************
      20       37  *************************************
      30       19  *******************
      40       12  ************
      50        6  ******
      60       14  **************
      70       11  ***********
      80        3  ***

Histogram of C3    N = 128

Midpoint    Count
    2.00        5  *****
    7.00       11  ***********
   12.00       10  **********
   17.00       23  ***********************
   22.00       14  **************
   27.00       12  ************
   32.00        7  *******
   37.00        6  ******
   42.00        6  ******
   47.00        3  ***
   52.00        3  ***
   57.00        7  *******
   62.00        7  *******
   67.00        7  *******
   72.00        4  ****
   77.00        3  ***
```

FIGURE A5

SHAPIRO - WILKS TEST ON KENT ONSET DATA

```
MTB > nscore c1 c2
MTB > plot c1 c2
```

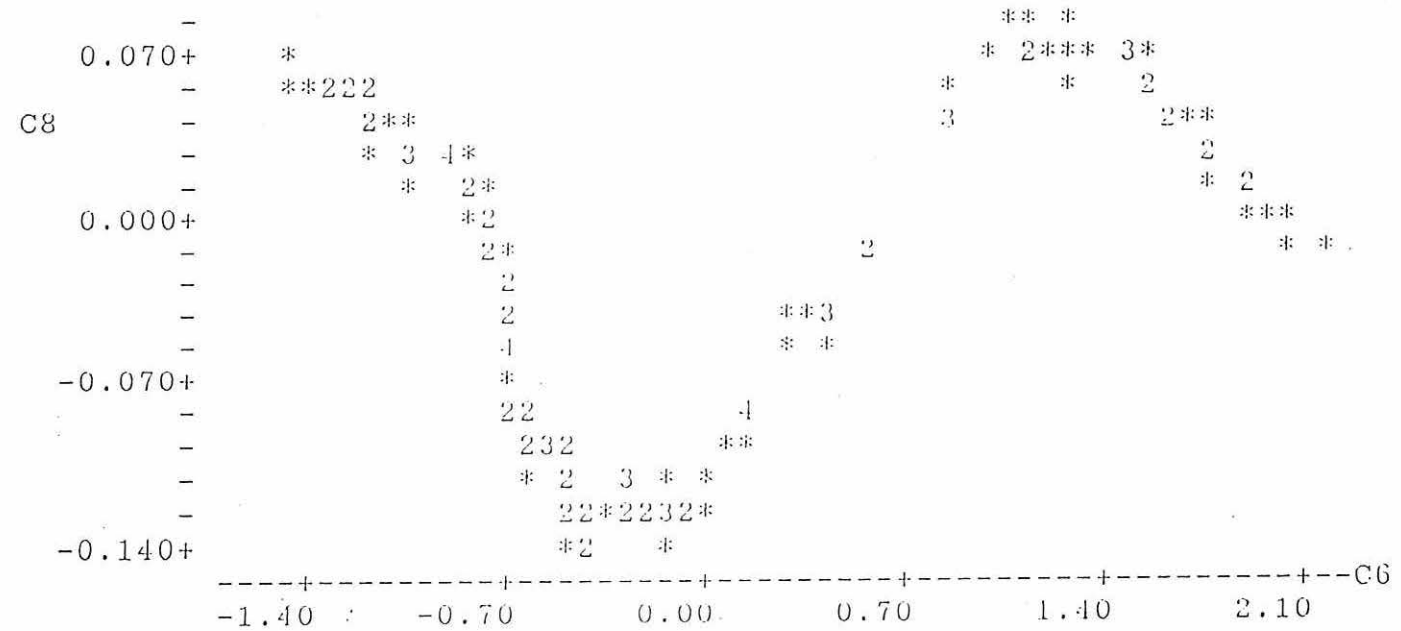



```
MTB > corr c1 c2

Correlation of C1 and C2 = 0.958
MTB > exec 'pub:nscore'
number of observations (at least 3) :-
The correlation coefficient should be at least k63
to be normally distributed at the 5% significance level.
MTB > print k63
K63       0.990154
MTB > & not normally distributed
```

FIGURE A6

FOULKES METHOD - KENT DATA

```
MTB > sort c1 c3
MTB > set c4
DATA> 1:128
DATA> end
MTB > let c5=(c4-1/2)/128
MTB > let c6=(c3-mean(c3))/stdev(c3)
MTB > cdf c6 c7;
SUBC> normal x s.
MTB > let c8=c7-c5
MTB > plot c8 c6
```



CHAPTER 5

MODELS OF INHERITANCE APPLIED TO PSORIASIS

5.1 Introduction

The results of Chapter 4 gave rise to further questions on the nature of the familial patterns of psoriasis found. Simply saying that there is an increased incidence of psoriasis in relatives of psoriasis patients compared with that in the relatives of controls, and associating this with the age of onset in psoriasis patients, does not go far in providing an answer to the strength of the hereditary factor. Any analyses of the genetic factors are subject to further complexities in psoriasis, arising from the onset pattern with its delays and variability. Many family members may well have the genetic liability to the condition but may not yet have manifested psoriasis or been diagnosed as psoriasis patients. The latent carriers of the gene or genes are not yet detectable by any laboratory test.

The first part of this chapter reviews the literature for the findings of other researchers and the development of the application of genetics to psoriasis. Included are HLA association, twin studies, as well as segregation analysis and population studies.

The second part of this chapter applies specific genetic models to the data in this study. Firstly, by testing for the presence of a genetic component by comparing the prevalence of psoriasis in first degree relatives of psoriasis patients with those of controls. Secondly, by trying to fit monogenic autosomal dominant and recessive models using segregation analysis of siblings. Thirdly, as a result of the outcome of the segregation analysis, by fitting polygenic and multifactorial models to the data. All the modelling was carried out separately on those above and below 40 years at onset, as well as the data as a whole, for comparison with other studies. The genetic correlation between early and late onset was also estimated.

5.1.1 Early Years of Genetics

The nature-nurture debate has existed from the time of the Greek natural philosophers. Simple Mendelian genetics arose out of the experimentation of Mendel (1822-1884) who showed that, when certain phenotypic changes are being considered, they can be divided into a small number of types of inheritance, always passed down from the parents to the progeny in the same ratios. For other phenotypic traits, where for example continuous measurements are involved, this approach was found to be inappropriate. Francis Galton (1822-1911) quantified these traits without explaining the cause. He specifically found that, if the trait was of a highly heritable nature, that is, little influenced by environmental factors, then the correlation between phenotypic values of parent and offspring approaches one half (Galton's Law).

5.1.2. Development of the Study of the Genetics of Psoriasis

Reporting of familial concentrations of psoriasis have led to suggestions that genetic factors play an important aetiological role. Researchers have attempted to fit different types of models to familial data. The study of twins is usually found to be particularly valuable in any assessment of the genetic role and this has yielded useful information in psoriasis. Segregation analysis, pedigree analysis, population analysis, serological analysis and, more recently, DNA analysis have also been undertaken.

5.1.2.1 Twin studies

Twins are one of two types, monozygotic (MZ), or identical, which are genetically the same, coming from a single zygote and dizygotic (DZ), where they are only like siblings in terms of genetic similarity because they are from two separate zygotes. The expectation would be that, if the aetiology is largely controlled by genetic factors, then MZ twins would demonstrate a higher concordance of the presence of psoriasis than DZ twins. Some indication of the degree of the contribution of environment, to the aetiology can be deduced, since

MZ twins would be expected to have 100% concordance, if the environment played no role.

Watson et al (1972) reviewed the research of others on twin studies, and in total he found concordance rates for 35 MZ and 33 DZ twin pairs reported, in which psoriasis was present in at least one twin. They found that 22 (63%) of the MZ twin pairs were concordant, that is, both members of the twin pairs had psoriasis, while only 7 (21%) of the DZ twin pairs were concordant, which is significantly different ($p < 0.01$) and this indicates a strong genetic component. They also concluded that the absence of 100% concordance in the MZ pairs indicated the presence of non-genetic influences in the aetiology of psoriasis.

Farber and Nall (1974) subsequently found a psoriasis concordance rate of 56/80 (70%) in MZ twin pairs compared with 14/60 (23%) of DZ twins, in a study in California, U.S.A. Brandrup et al (1978, 1981), using the Danish Twin Registry, found similar results to these high concordance rates for MZ twins compared with DZ twins, of 56% and 14% respectively. Lomholt (1963) found that 15/27 (55.6%) of MZ twin pairs were concordant for psoriasis, but these were taken from a mixture of his own data and that from the literature.

The data in the present study contained no known twins and therefore comparison with the other studies was not possible. With the exception of Brandrup et al (1978,1981), the studies above mostly have a larger proportion of MZ twins in them than are present in a normal population and factors such as delays in manifesting psoriasis were not included. These studies can, at best, give a qualitative indication for the genetic influence in the aetiology of psoriasis compared with environmental factors. Watson et al (1972) stated that there was a suspected bias in a "tendency to report concordant pairs". They also stated that twin studies were indicative of a hypothesis of multifactorial inheritance, which will be discussed later in this Chapter.

The most recent research on psoriasis in twin data has been conducted by Duffy et al (1993) using a postal questionnaire sent to individuals on the Australian Twin Registry. They used the technique of Martin and Martin (1975) to identify identical twins, and found a concordance rate of 35% in MZ twins and

12% in DZ twins. This was compared with the results of Brandrup et al (1978,1981), and they concluded that concordance rates were lower in the Southern Hemisphere, although the heritability of 80% was about the same, and that non genetic factors, such as climate play a role in the expression of psoriasis.

5.1.2.2 HLA antigens

Human leukocyte antigens (HLA) are present on the surface of cells in the body and are important for the immunological response mechanisms governing susceptibility to the disease. These HLA antigens are associated with a major histocompatibility complex which lies on the short arm of chromosome 6 and are heritable (Kingston, 1989). Four loci for these antigens are known in humans. These are the class I antigens A,B,C, and the class II antigens D/DR, where DR infers the serologically defined antigens related to the D locus. Each individual has alleles (affected genes) associated with each locus according to the genotypes of the parent, that is, 2 alleles, one from each parent at each site. However, a haplotype is transmitted by one parent in the gamete and is the combination of HLA genes present physically in one part of the same chromosome. Two chromosomes are required for each genotype and thus each individual has a combination of two haplotypes (Zachariae, 1986).

Many clinical disorders demonstrate an association with a particular HLA type, implying that this can be used as a marker for the actual disease gene. This association with HLA types does not imply genetic linkage when two gene loci are found in a position physically close together on the chromosome. HLA typing can be used to a certain extent to predict the risk of disease occurring within a family, or a population, by establishing the associated HLA haplotype present. For example, a disease gene located near the HLA complex of genes on chromosome 6, will be associated to a certain HLA haplotype in one affected family, but this same haplotype may not necessarily be relevant for people who are not members of that family (Kingston, 1989).

Studies on HLA typing have helped establish subgroups of psoriasis patients and showed the strength of association (as a relative risk) of developing

the disease. This will vary with the racial origin or even the familial origin of the individual. Association of certain HLA antigens with psoriasis as found by other researchers is summarised below. The present study carried out no HLA association analysis, but this section is included because identification of HLA associations may indicate the genes or groups of genes involved in psoriasis. Where early onset or late onset is specified in the research of others, it is not directly related to the two onset distributions as presented in Chapter 4, except for that of Henseler and Christophers (1985), who have identified two types of psoriasis: Type I with onset < 40 years and positive family history and Type II with onset $\geq$ 40 years and negative family history. In most of the studies quoted, early onset usually means before the age of 20 years and late onset after this age, and the researchers had been unaware of the two distinct onsets as defined above.

The HLA associations reported by those who have studied psoriasis patients, regardless of age of onset are:- HLA-B13 and HLA-B17 (White et al, 1972; Russell et al, 1972). HLA-B13, HLA-B17 and HLA-B37 (Karvonen, 1975; Svejgaard et al, 1975). HLA-DR7 (Tsuji et al, 1979). HLA-Cw6 (Tiilikainen et al, 1980; Asahina et al, 1991).

The HLA associations with an early onset are:- HLA-B13, HLA-B17 and HLA-B37 (Nordberg-Iversen and Zachariae, 1984). HLA-B13, HLA-B17, HLA-B37 as a secondary association with Cw6 (Svejgaard et al, 1974). Strong association with HLA-Cw6 (Heneseler and Christophers, 1985).

Lack of the HLA associations identified with a late onset are:- HLA-B13, HLA-B17, HLA-B37, HLA Cw6 by the authors quoted in the early onset associations. Also, HLA-Cw2 and HLA-B27 had a weak association in late onset (Christophers and Henseler, 1985).

These findings of an association of class I antigens with Type I psoriasis (early onset), and a weaker association of HLA-Cw2 and HLA-B27 with Type II psoriasis (late onset), have been recently confirmed by Schmidt-Egenholf et al (1993). They also reported that they had discovered a significant association of class II antigens with Type I (early onset) psoriasis, when detected on the DNA level, rather than by serological analysis.

The type of psoriasis (excluding pustular psoriasis) which had HLA associations were:- Guttate psoriasis - HLA-B13, HLA-B17 (Tiilikainen et al, 1980). Psoriasis vulgaris - HLA-Cw6 (Ozawa et al, 1988), HLA-DR7 (Tsuji et al, 1979). However, a lack of association with HLA-B13, HLA-B17 with flexural psoriasis was also reported (Karvonen, 1975).

Nordberg-Iversen and Zachariae (1984) demonstrated the early onset association with B13, B17 and B37 by means of an age at onset distribution which was skewed to the right and had a peak at about 15 years of age. A second distribution lacking these associations appeared from their figure to have a bimodal onset distribution with modes at 25 years and 55 years approximately, but they did not comment on this bimodality. (This is discussed in section 5.2.3.)

Marcussen et al (1981) suggested, from all the evidence to date in the literature, that two susceptibility genes may be operating in psoriasis, one located in the C region and one in the DR region. This combined the two major associations of Svejgaard et al (1975) and Tsuji et al (1979). Fry (1988), in a review article, suggested that there may well be two genes, one associated with the class I antigens, such as that at the CW6 region and the other associated with the class II antigens, at the DR7 region, but they do not appear to apply to every population studied.

The strongest association demonstrated so far is that with Cw6 where a relative risk (RR) overall of 25 was demonstrated by Henseler and Christophers (1985) using data from Tiilikainen et al (1980). They used the formula $RR = (f_p/f_c) \times (1-f_c)/(1-f_p)$ where f_p and f_c were proportions of antigen in patients and controls respectively. They also found an RR of 44.5 for their Type I (early onset) psoriasis and a RR of 7.3 for their Type II (late onset) psoriasis.

5.1.2.3 Pedigree and segregation analysis

Some of the early reports on psoriasis inheritance in families suggested that a monogenic autosomal dominant gene was responsible while others suggested that

the pattern they found was due to a monogenic autosomal recessive gene or possibly double recessive genes.

Hoede (1957) analysed a mixture of other physicians' data plus his own family data which led him to a hypothesis of a monogenic dominant pattern of inheritance with no differences between the sexes. Romanus (1945) also came to this conclusion of dominance with no sex difference. Ward and Stephens (1961) carried out a study of a large family in Utah, U.S.A. and concluded that their findings could be attributed to a monogenic autosomal dominant inheritance. Abele et al (1963) found similar results in a study in North Carolina, U.S.A. Later, Kimberling and Dobson (1973) suggested that the mode of inheritance could be autosomal dominant, but with a reduced penetrance.

Steinberg et al (1951) suggested that a single autosomal dominant gene with incomplete penetrance could explain Hoede's data. However, they proposed a hypothesis that there may be two unlinked autosomal recessive genes, based on their own findings, which gave results compatible with this approach. This will be discussed in section 5.2.2.3.

Lomholt (1963) found that his data could possibly be attributed to either a monogenic dominant inheritance with failing manifestations model but ruled out a single or double recessive model. His data was later re-analysed, as was that of Hellgren (1967) from Sweden, by Ananthakrishnan et al (1973,1974) who showed that the inheritance patterns could be explained by multifactorial models.

Segregation analysis will be enlarged and the results of this study considered later in this Chapter (section 5.2).

5.1.2.4 Population studies

If no simple genetic pattern can be demonstrated for a disease, an alternative model is to assume that there are numerous determinants both inherited and environmental (Kingston,1989).

The "liability" in a population affected by a certain disease is a measure of the critical complement of factors required for manifestation of the condition, including innate tendencies and external influences (Falconer, 1965). If many

factors are assumed, where none are particularly dominant, there will be a mean liability in any population. The central limit theorem in statistics can then be applied with expression of the liability as a normal distribution pattern. The majority of individuals usually have a low susceptibility to a condition, but when a "threshold" of liability is exceeded, the disease is manifest (Carter 1961). All the relatives of a person with the condition will show a shift in the mean liability, from that of the general population, with a higher proportion than the rest of the population being in the critical area of the normal distribution beyond the fixed threshold. The liability to manifest psoriasis is the sum of all the factors, genetic and environmental, which make an individual more or less likely to develop the condition. The liability to psoriasis in a population is a continuous variable, with a threshold value above which individuals are identified as having psoriasis in a once and for all diagnosis. This threshold leaves an area in the upper tail of the normal distribution representing the prevalence in the general population (or a suitable control group), and in the relatives of psoriasis patients.

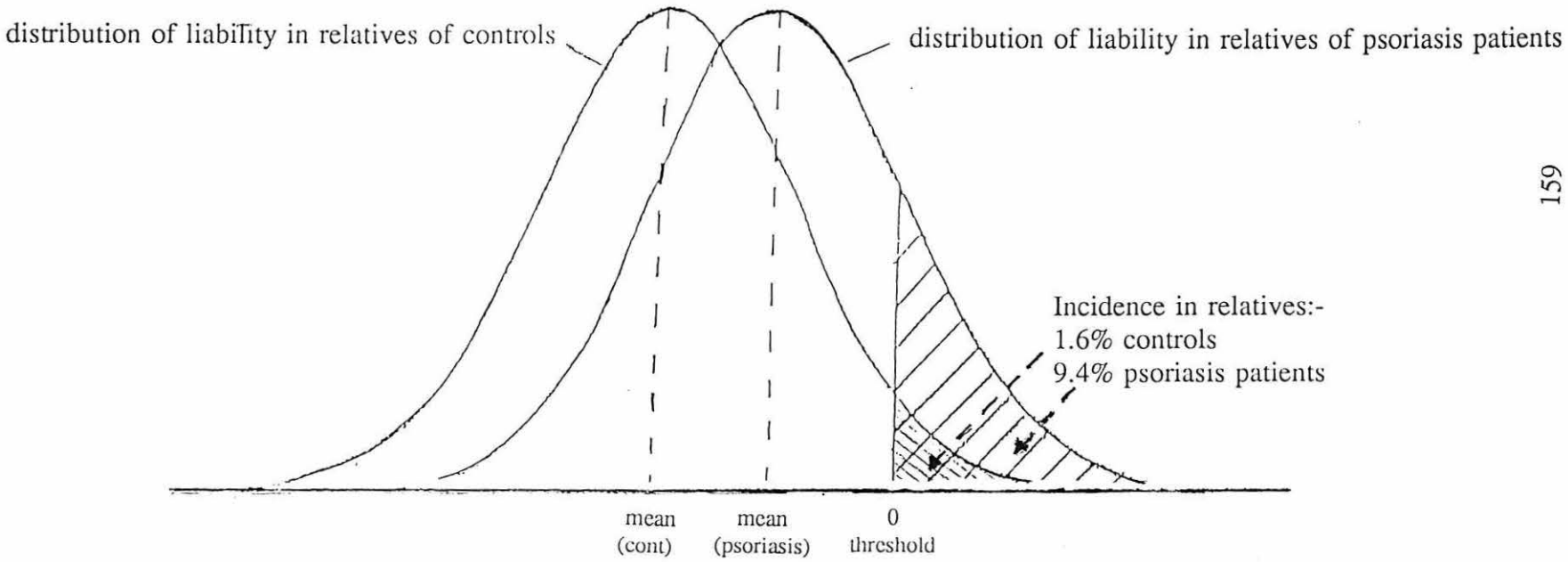
Here, the assumption is made that psoriasis is not transferred by a single major gene, as this would cause discontinuity in liability. The mean liability is measured in standard deviation units from this threshold and can be used for comparison purposes.

Figure 1 (p159) demonstrates this distribution of "liability" and the shift in means between two groups. One distribution is that of the frequency of psoriasis in the relatives of the psoriasis patients, which is found in the present study to be 9.4%. The other is that in the relatives of the control group of this study of 1.6% (section 3.1.4.4).

The majority of researchers have found that their data fitted a polygenic mode of inheritance, for example, Andressen and Henseler (1982). While Watson et al (1972) and Ananthakrishnan et al (1973,1974) quantified the "heritability" under the assumptions of the multifactorial model applied to psoriasis, using the methods of Falconer (1965). Fry (1988) was of the opinion that simple monogenic types of inheritance had been excluded in psoriasis.

FIGURE 1

Distributions of liabilities, with differing means for the relatives of the controls (or general population) and those of psoriasis patients, with reference to a fixed threshold.



The multifactorial model and its assumptions, along with the heritability estimates based on these will be discussed in detail in section 5.2.4.

5.1.2.5 Current research

Elder et al (1994) quote Lomholt (1963) in commenting on the current state of investigation into the genetics of psoriasis, "that psoriasis is genetically conditioned is beyond doubt, but, when the mode of inheritance appears to have been almost demonstrated, it again slips out of the pattern of fixed rules!". Risch (1990) determined whether there was one or more genes involved by examining the risk ratio (λ_R), the risk of getting psoriasis in a relative of degree R in relation to the general population. By this method he found that the ratio of the risk in a first degree relative, compared to the risk for a second degree relative, decreases by a factor of two where there is a single dominant gene operating. Elder et al (1994) examined Hellgren's (1967) data and found that this risk decreases by much more than a factor of two with each degree of relationship, for example it decreased by a factor of 6 in going from first degree relatives to second degree relatives, making Hellgren's data consistent with a multilocus mode of inheritance. Similarly, they applied this method to Lomholt's (1963) data, and found evidence which again supported a multilocus model. They state that they, "for the first time have provided formal genetic evidence for multilocus involvement in this disease".

These authors suggest that, although psoriasis is a highly HLA associated disease, which also appears to be heritable, other factors are involved. They estimate that only about 1 in 10 individuals who have an HLA association, for example a Cw6 antigen, actually develop the disease. They concluded that this, and all the evidence of HLA antigen studies, means that there is a possibility of other genes being involved, not necessarily associated with HLA. Also, they state that they are aware of environmental influences on the manifestation of psoriasis.

They formulated a hypothesis about the heredity of psoriasis calling it the "oligogenic hypothesis", which states that one or two genes are required in addition to HLA, while other minor genes may serve to modulate the severity. They advocate the usage of oligonucleotide probes, a newly developed form of DNA probe, which are able to detect disorders confined to one or a few base pairs of genetic units on a chromosome.

On this basis they employed the technique of "lod score analysis" where lod score = ($\log_{10}$ Odds Ratio) that a particular pattern of inheritance of a genetic marker, for example a specific HLA locus, would be observed if the marker were located physically close to the disease gene, that is linked to the disease gene. However this approach was inconclusive, but they propose that this could be helpful in identifying non-HLA linked loci.

Finally they call for using a "candidate gene" approach to locating and finding the implicated gene or genes in the human genome by means of an educated guess. This appears to be a forerunner for a large study on familial psoriasis, including clinical examination and DNA sampling of members of psoriatic families in the U.S.A. This study has arisen out of results of a study by Nair et al (1993) who state that they have eliminated a single autosomal dominant gene model in psoriasis.

Traupe et al (1992) studied the birth weight of children who had mothers and fathers who were psoriatic. They examined 78 in each category and found that there was an average birth weight of 3,445 grams when the father was affected, which was higher than that of 3,217 grams when the mother was affected. This shows a statistically significant increase ($p < 0.005$) if the father is affected. They further studied Lomholt's (1963) data and concluded that there was a significantly higher penetrance of psoriasis if the father was either psoriatic or presumed to be a genotype carrier. They found that males with psoriasis have 28.4% of affected children compared with mothers having 20.8% of affected children ($p < 0.02$). They concluded that these findings provided evidence for "genomic imprinting" which is a recently discovered phenomenon in humans

where the expression of the genotype in offspring is influenced by the sex of the parent in that the gametes are modified. The findings of Traupe et al were emphasised, by Happle (1991), as being a possible explanation for certain types of psoriasis, for example, "linear psoriasis". Traupe et al (1992) state that "in the past 2 different models have been proposed (1) monogenic dominant transmission with incomplete penetrance and (2) polygenic inheritance involving essentially equal contributions from a number of genes". However, the research of others has also suggested a single or double recessive mode of inheritance.

A possible clue for finding a psoriasis susceptibility gene has come from Rosbotham et al (1994). They examined the pedigree of a family who had both psoriasis and hereditary multiple exostoses (HME) and suggested that since a major gene locus for HME has been mapped to chromosome 8q, it may be possible to look for an association with this for psoriasis for alternative gene sites. They state that this concurs with reporting of fits to a dominant gene model as suggested by Abele et al (1963) and partially by Lomholt (1963).

Swanbeck et al (1994) have carried out a survey of 5197 psoriasis patients in Sweden who are members of the Swedish Psoriasis Association. They stated that older probands may be under-represented because they would be less likely to become members of the Swedish Psoriasis Association. The objective of the study was to determine whether it was possible to differentiate between a monogenic autosomal dominant and an autosomal recessive mode of inheritance, using first degree relatives of the members. They concluded that their data was consistent with the presence of a monogenic autosomal recessive gene. Data on all first degree relatives was presented and they found that 36% of the probands reported having at least one parent with the condition. Where there was an affected proband they reported 16% of the siblings with psoriasis. The penetrance of the gene for a single recessive mode is expressed in their study as the fit of the data of 86.9% (father) and 88.9% (mother) to that expected from the model in which 1 parent has psoriasis ($p < 0.05$). The penetrance is expressed as 93.7% for that expected when 0 parent has psoriasis ($p = 0.25$). This was thought

to demonstrate a good fit of the model for a single recessive gene. These figures give no evidence to support a theory of genomic imprinting in the population studied, because the percentage penetrance in the offspring of affected fathers would be expected to be higher than that for affected mothers.

On the assumption of a monogenic recessive mode of inheritance, they suggest that families can be counselled according to this. If one parent has psoriasis, they propose that the risk of children developing the disease is 15%. (They found that 15% of the children of their probands were affected, without correction for delayed onset.) If no parent has psoriasis, and there is a progeny with the disease, they propose that 20% of the siblings would develop the disease. (They found that 16% of siblings of probands in their study had the condition.)

The findings of Swanbeck et al (1994) are, however, in conflict with the research of others into the presence of psoriasis in the Scandinavian population. The classical study of Hellgren (1967), in which he examined entire populations of the districts of Norrbotten, Kristianstad, Jämtland and Skaraborg (n = 38,670) in Sweden, has been re-analysed by others and found to demonstrate multifactorial or a multilocus mode of inheritance. For example, Ananthakrishnan et al (1973) applied Falconer's (1965) model and found that first degree relatives had a heritability of 52%, consistent with a multifactorial inheritance model. The data on the Faroe Islands population (Lomholt, 1963) was found by Ananthakrishnan et al (1974) to have heritabilities of 91% for all first degree relatives, and was concluded to be indicative of a multifactorial inheritance model. Elder et al (1994), as previously stated, have found evidence for a multilocus model in Hellgren's data and that of Lomholt.

5.2 **Genetic models used in this study**

As stated earlier, no pedigree or serological or DNA analyses was carried out in the present study. Segregation analysis was employed to elucidate genetic patterns between parents, siblings and children. Monogenic, double recessive and

multifactorial inheritance models were applied. Overall, the main difficulty in assessing any genetic pattern is with the delayed onset of psoriasis and also with those patients who have latent psoriasis, that is, who have the predisposition but who never manifest the condition.

5.2.1 The Data

A new data file was created for all those whose family history with regard to presence or absence of psoriasis in first degree relatives could be ascertained, and this was available on the questionnaires. It resulted in full family histories of parents, siblings and children of 413 psoriasis patients and 283 controls, collected at the time of clinical examination. The average age of psoriasis patients was 9 years older than the age of onset (section 4.4) and this complicates the interpretation of the family history, when comparing age of onset in psoriasis patients with age in controls, as this lapse of 9 years means that more relatives of psoriasis patients will have had time to manifest the condition. This difference was corrected by adding 9 years to the ages of controls when family history was being considered. For those psoriasis patients whose exact age of onset was not known, it was possible to code whether they were <40 or ≥ 40 years age of onset, using this 9 years correction factor, and their age at time of examination.

5.2.2 Segregation Analysis

A preliminary segregation analysis of the data gave a comparison between the prevalence of psoriasis in the first degree relatives of psoriasis patients and controls. The data was divided up into early and late onset and the results are presented in Table 1 (p167). This demonstrates that there are higher percentages of affected relatives associated with early onset than with late onset, and that the differences between affected parents, siblings and children of psoriasis patients and the corresponding affected relatives in controls are all significant ($p < 0.01$ to $p < 0.0001$). This is strongly indicative of a genetic role playing a major part in the liability to psoriasis, particularly at early onset. This division between early and late onset types has been documented in this work for the first time.

Results of further segregation analysis applied to this data are given in Table 2 (p169) and Table 3 (p170). These again, unlike those obtained previously by others, have been divided up into early and late onset groups. Also, to detect any possible differences in sex linkage, into male and female patient groups.

Because of the range in the age of onset in the patient, the prevalences are all underestimates of what they would be if all patients and relatives had a full lifespan. This is particularly marked for the families of early onset patients. It is not possible to correct for ages of relatives in the manifestation of psoriasis because the data does not contain this information. Watson et al (1972) had this information and used the method of Morton (1959) to correct for delays in onset in their psoriasis data. The formula used the age in the siblings, given by

$$\int f(z)\ G(z)\ dz$$

where z is the number in the siblings, f(z) is the frequency of the siblings who die at a certain age and G(z) is the frequency of these who have psoriasis. At the earlier ages $f(z) \rightarrow 0$ and $G(z) \rightarrow 0$, while in later ages $f(z) \rightarrow 1$ and the integral tends to the true proportion who will ever manifest psoriasis.

Morton states that "for a common trait, incomplete penetrance so complicates the analysis that the methods of this paper are not always applicable .... it is not always clear how adequate this model for the segregation ratio would be". Nevertheless, Watson et al (1972) calculated (without giving details) that the penetrance in psoriasis would be reduced to about 81% when accounting for the delay in age of onset. These researchers gave prevalences of 7.5% of siblings affected when no parent had psoriasis and 15% of siblings affected when 1 parent had the disease. They found no difference between the sexes in the prevalence of psoriasis in all the relatives (4.4% of relatives of male probands, compared with 4.7% of relatives in female probands) and so grouped them together for segregation analysis.

Table 2 (p169) gives the results in the present study for the early onset psoriasis group when 0 parent is affected, of 8.4% (5.3% for males, 11.4% for females). If 1 parent is affected, then 14.8% of the siblings were affected (14.9% for males, 14.6% for females). Similarly, Table 3 (p170) gives results for late onset, when 0 parent is affected of 4.1% (5.1% for males, 3.2% for females). When 1 parent was affected, 8.5% of the siblings were affected (9.1% for males, 8.3% for females).

Over all psoriasis patients, 6.6% of the siblings are affected when 0 parent is affected and 13.6% of the siblings are affected when 1 parent is affected (Table 3, bottom). These results are similar to those obtained by Watson et al.

In view of the absence of strong evidence of sex differences, and to maximise the numbers involved, the segregation analysis models were applied to the combined data for the two sexes.

5.2.2.1 Monogenic autosomal dominant model

A simple autosomal dominant inheritance pattern would be expected to give a result of 50% of the siblings of the psoriasis patients developing psoriasis, when 1 parent is affected. The percentage of affected siblings of psoriasis patients when 1 parent is affected is 13.6% for all onsets. The corresponding figure for early onset psoriasis patients is 14.8%, while that for late onset is 8.5%.

The results give percentages in the siblings of psoriasis patients, when 1 parent is affected, which are substantially less than 50%, even if possible correction for delay in onset were considered. This does not support a hypothesis of a single autosomal dominant gene operating in psoriasis.

The percentages in each of the first degree relatives should be approximately the same under this model. For early onset 16.3% of parents are affected, 10.5% of siblings and 9.7% of children. For late onset, the corresponding results are 6.5%, 5.1% and 8.5%, while those for all onsets are 12.8%, 8.5% and 9.1%. These percentages in the children are not reliable because many will not yet have manifest the condition. The differences between parents and siblings is significant for early onset ($p < 0.01$), not significant for late

TABLE 1

A comparison between the prevalence of psoriasis in first degree relatives of psoriasis and control patients

(A_r, A_c and N_r, N_c are the affected (Aff.) and total no. of relatives of psoriasis and control patients.)

	Psoriasis Patients			**Control Patients**				
	A_r	**N_r**	**% Aff. ± S.E.**	**A_c**	**N_c**	**% Aff. ± S.E.**	**χ^2, df=1**	**p-value**
Early onset								
Parents	87	534	16.3 ±1.6	9	322	2.8 ±0.9	36.8	<0.0001
Siblings	71	675	10.5 ±1.2	2	349	0.6 ±0.4	34.4	<0.0001
Children	27	278	9.7 ±1.8	4	147	2.7 ±1.4	7.0	<0.01
Tot. Rel.	185	1487	12.4 ±0.9	15	818	1.8 ±0.5	74.9	<0.0001
Late onset								
Parents	19	292	6.5 ±1.4	4	244	1.6 ±0.8	7.7	<0.01
Siblings	20	393	5.1 ±1.1	5	316	1.6 ±0.7	6.3	<0.01
Children	23	272	8.5 ±1.7	2	225	0.9 ±0.6	14.8	<0.0001
Tot. Rel.	62	956	6.5 ±0.8	11	785	1.4 ±0.4	27.7	<0.0001

TABLE 1 (cont)

A comparison between the prevalence of psoriasis in first degree relatives of psoriasis and control patients

(A_r, A_c and N_r, N_c are the affected (Aff.) and total no. of relatives of psoriasis and control patients.)

	Psoriasis Patients			**Control Patients**				
	A_r	**N_r**	**% Aff. ± S.E.**	**A_c**	**N_c**	**% Aff. ± S.E.**	**χ^2, df=1**	**p-value**
All onset								
Parents	106	826	12.8 ±1.2	13	575	2.3 ±0.6	41.9	<0.0001
Siblings	91	1068	8.5 ±0.9	7	665	1.1 ±0.4	38.9	<0.0001
Children	50	550	9.1 ±1.3	6	372	1.6 ±0.7	19.6	<0.0001
Tot. Rel.	247	2443	10.1 ±0.6	26	1603	1.6 ±0.3	110.8	<0.0001

TABLE 2

Segregation analysis of siblings (Sibs) and parents (Par.) for different mating classes of parents, where 0,1,or 2 parents are affected (Aff.) and for male and female psoriasis patients at early onset

Early onset	Mating class	Aff. No. of Par.	Total No. of Par.	Aff. No. of Sibs	Total No. of Sibs	% of Sibs Aff.
male	0	0	170	12	225	5.3
	1	37	74	13	87	14.9
	2	0	0	0	0	0
female	0	0	192	27	237	11.4
	1	48	96	18	123	14.6
	2	2	2	1	3	33.3
All males and females	0	0	362	39	462	8.4
	1	85	170	31	210	14.8
	2	2	2	1	3	33.3

TABLE 3

Segregation analysis of siblings (Sibs) and parents (Par.) for different mating classes of parents where 0,1, or 2 parents are affected (Aff.) and for male and female psoriasis patients at late onset, and all onsets

Late onset	Mating class	Aff. No. of Par.	Total No. of Par.	Aff. No. of Sibs	Total No. of Sibs	% of Sibs Aff.
male	0	0	124	8	158	5.1
	1	6	12	1	11	9.1
	2	2	2	2	3	66.7
female	0	0	132	6	185	3.2
	1	11	22	3	36	8.3
	2	0	0	0	0	0
All males and females	0	0	256	14	343	4.1
	1	17	34	4	47	8.5
	2	2	2	2	3	66.7
All onsets and both sexes	0	0	618	53	805	6.6
	1	102	204	35	257	13.6
	2	4	4	3	6	50.0

onset ($p = 0.22$) and for over all onsets is significant ($p < 0.01$). Although the percentages are similar for late onset, this is not strong evidence of a monogenic autosomal dominant mode of inheritance.

5.2.2.2 Monogenic autosomal recessive model

In autosomal recessive inheritance, carriers of the gene (heterozygotes) remain healthy and it is the homozygote which defines the condition, which means that in a recessive mode of inheritance, the condition can often just appear in one generation.

For a simple recessive gene theory, with complete penetrance, 25% of siblings of affected probands overall would be affected in the absence of affected parents, when those parents are both heterozygous for the condition The percentage in the siblings is 50% in the presence of 1 affected parent (Watson et al, 1972). This is understood to be when 1 parent is homozygous for psoriasis and the other is heterozygous for psoriasis.

The results of this study, when 0 parent is affected is that 6.6% of all the psoriasis patients' siblings are affected. When early onset in the patient is considered, then 8.4% of the patients' siblings are affected and 4.1% for late onset probands. This is substantially lower than the 25% required for the single recessive gene model. When 1 parent is affected, the observed results are that 13.6% of all the patients' siblings are affected, with 14.8% for early onset and 8.5% for late onset. These percentages are not sufficient to meet the requirements of the model.

Under this model, when 2 parents are affected, then 100% of all the patients' siblings would be affected. The percentages found in this study are 50% of siblings for over all ages of onset in the psoriasis patients. That for the siblings of early onset in the psoriasis patients is 33.3% and for late onset 66.7%. However, only 2 matings are involved so these results need to be treated with care.

Since recessive conditions can miss a generation, then some patients would not have an affected parent, but 25% of the siblings of patients would

be expected to be affected in a single recessive gene model, meaning that more siblings of patients would be expected in this case to have psoriasis than parents.

The percentage of affected parents in this study over all onsets in the psoriasis patients is 12.8%. That for early onset is 16.3% and late onset 6.5%. If these are compared with the results for affected siblings the equivalent results are 8.5%, 10.5% and 5.1% respectively, indicating greater numbers of parents affected than siblings.

There is little evidence in these results, to support a single recessive gene theory operating in psoriasis.

5.2.2.3 Two unlinked autosomal recessive genes model

In the model for two unlinked autosomal recessive genes, the pair of alleles are represented by aabb, and the situation where no alleles are involved is given by AABB. Let the frequencies of a and b be given by p and r respectively, the frequency of A (unaffected) becomes (1-p) = q and the frequency of B (unaffected) becomes (1-r) = s. If pr is the observed prevalence of psoriasis in the parents, that is, affected parents to total parents, then if we write pr = m and 1-pr = n, then when both parents are affected this gives a relative frequency of m^2 (homozygous), and 2mn when 1 parent is affected (heterozygous) and n^2 when 0 parents are affected (no allele involved) (Steinberg et al, 1952).

This is equivalent to the Hardy Weinberg Equilibrium for the presence of alleles at two loci, for a double recessive model, which is:-

$$p^2r^2 + 2pr(1-pr) + (1-pr)^2 = 1$$

Two methods of testing for the presence of two unlinked autosomal recessive genes were suggested by Steinberg et al. The first is a comparison between the expected numbers and the observed numbers of those affected in the psoriasis patients within the different mating classes in the parents. The

second is a test of whether there is a significant difference between the expected ratio of numbers of siblings affected when 1 parent has psoriasis to the number of siblings affected when 0 parent has psoriasis and the observed ratio of these affected sibling groups.

In Table 1 (p167) of this study, the prevalence m in the parents is 87/534 (16.3%) for early onset psoriasis patients, 19/292 (6.5%) for late onset psoriasis patients and 106/826 (12.8%) over all ages of onset in these patients. Using the assumption that the frequency of the alleles are equal in the population, that is p = r, then q and s can be estimated. The values of p may be taken as 0.163/r (early onset), 0.065/r (late onset) and 0.128/r (over all onsets).

Then,

$$q + s = 2 - p - r$$
$$= 2 - m/r - r$$

This expression is a maximum when r = √(prevalence in the parents), that is √0.163 = 0.40 for early onset, √0.065 = 0.25 for late onset and √0.128 = 0.36 for all onsets. From this, and p = r, the values of the expected relative frequencies

$$m^2 = p^2r^2$$
$$2mn = 2pr(1 - pr)$$
$$n^2 = (1-pr)^2$$

may be calculated.

The results of applying the first test for an autosomal double recessive model in the psoriasis patients in this study, are given in Table 4 (p174). Here the expected numbers of these patients are those when m^2 (2 parents affected), 2mn (1 parent affected, and n^2 (0 parent affected) are multiplied by the total number of patients, in each age of onset category, if this mode of inheritance were in operation. These total number of psoriasis patients can also be

TABLE 4

Observed and Expected numbers of psoriasis patients, in each mating class, for testing for double recessive inheritance model.

(n_{tot} = total number of patients in each age of onset category).

		Expected		Observed number	
		Proportion	No.		
Early Onset				n_{tot}= 267	
No. of Aff. Parents	2	m^2=0.027	7.2	1	χ^2 on 1 d.f. = 7.55 (p < 0.01)
	1	2mn=0.273	72.9	85	
	0	n^2=0.701	187.2	181	
Late Onset				n_{tot}= 146	
No. of Aff. Parents	2	m^2=0.004	0.6	1	χ^2 on 1 d.f. = 0.32 (p = 0.57)
	1	2mn=0.122	17.8	17	
	0	n^2=0.874	127.6	128	
All Onsets				n_{tot}= 413	
No. of Aff. Parents	2	m_2=0.016	6.6	2	χ^2 on 1 d.f. = 4.35 (p < 0.05)
	1	2mn=0.223	92.1	102	
	0	n^2=0.760	313.8	309	

obtained from Tables 2 and 3 (p169 and p170) by dividing the total numbers of parents by 2. The observed numbers are the those actually found in each mating class, of patients with early and late onset as well as over all onsets. When a χ^2 test for goodness of fit was applied, the data for affected parents associated with early onset was a poor fit ($p < 0.01$), as was the data for all onsets ($p < 0.05$). These were largely the result of substantial differences between the observed and expected numbers when both parents were affected at early onset.

In contrast to this the model for late onset was a very good fit to the data ($p = 0.57$). The χ^2 test has 1 (=3-2) degrees of freedom (d.f.) since an additional constraint was introduced with the estimation of expected frequency p.

The second test for an autosomal double recessive model again uses the methods of Steinberg et al (1952) applied to the number of affected siblings of psoriasis patients when 1 parent is affected and when 0 parent is affected. These researchers presented the resultant frequencies of all the genes from each possible mating pattern and multiplied these by the homozygous fraction that would be present, to obtain the frequency of the genotype for each mating, that is, the homozygous recessive alleles. When totalled this results in $2p^3r^3(1-pr)$ for the frequency of the recessive alleles in the total population when 1 parent is affected and $p^2r^2(1-pr)^2$ when 0 parent is affected.

When the frequency of the recessive alleles in the total population is divided by the frequency of all the genes arising from the total matings, we obtain the ratio of siblings who would be expected to have psoriasis.

For 1 parent affected the ratio is:-

$$\frac{(1-pr)}{2(q+s)}$$

For 0 parent affected the ratio is:-

$$\frac{(1-pr)^2}{4(q+s)^2}$$

Therefore, the ratio of these two expressions is:-

$$\frac{2(q+s)}{(1-pr)}$$

Using the above formulae, the ratio of the numbers of siblings expected when 1 parent is affected and 0 parent is affected are found to be 2.85 ± 0.47 (S.E.) for early onset, 3.20 ± 1.01 (S.E.) for late onset and 2.94 ± 0.42 (S.E.) over all onsets (Table 5, p177). The equivalent ratio of the numbers observed are 1.76 ± 0.47 (S.E.) for early onset, 2.07 ± 1.31 (S.E.) for late onset and 2.06 ± 0.48 (S.E.) over all onsets, from Tables 2 and 3 (p169 and p170). The standard errors quoted here are approximations obtained, using the methods of Mould (1994). The differences in these ratios, given in Table 5 , indicate that for early onset the model fit is poor ($p < 0.05$). While the fit at late onset is good ($p = 0.39$) and for overall ages of onset the fit is marginal ($p = 0.07$).

Different methods of estimation of standard errors may produce slightly different results, but when the above method was applied to the results obtained by Steinberg et al (1952), the standard error found was similar to that of Steinberg et al, resulting in $p = 0.66$ compared to $p = 0.6$ in their paper.

To summarise, the results of both Table 4 and Table 5 indicate that early onset is inconsistent with a double recessive model, while that of late onset is a good fit using both tests under this model. The data for all onsets gives conflicting results.

TABLE 5

The expected and observed proportions and ratios of siblings of patients, who have psoriasis when 0 and 1 parent are affected, for testing for a double recessive model.

	EXPECTED RATIOS OF AFFECTED SIBLINGS			OBSERVED RATIOS OF AFFECTED SIBLINGS				
	1 Parent affected	0 Parent affected	Ratio of 1 to 0 parent ± S.E.	1 Parent affected	0 Parent affected	Ratio of 1 to 0 parent ± S.E.	Difference in Ratios	p-value
Early onset	0.351	0.123	**2.85 ± 0.47**	0.148	0.084	**1.76 ± 0.47**	**1.09**	**< 0.05**
Late onset	0.314	0.098	**3.20 ± 1.01**	0.085	0.041	**2.07 ± 1.31**	**1.13**	**= 0.39**
All onsets	0.339	0.115	**2.94 ± 0.42**	0.136	0.066	**2.06 ± 0.48**	**0.88**	**= 0.07**

5.2.2.3.1 Final comments

The data in this study can be demonstrated to be a reasonable fit to the two tests applied for a double recessive mode of inheritance, for late onset but not for early onset. It is possible that the assumption of equal frequencies of the two alleles does not hold, or that all possible mating patterns are not present in the population. Furthermore, monogenic dominant or recessive modes of inheritance were also rejected. These, together with the absence of 100% concordance between MZ twins (section 5.1.2.1) which indicates that environmental factors contribute to the aetiology of psoriasis, would suggest testing for a multifactorial mode of inheritance.

5.2.3 Distribution of the Age of Onset of Patients when None and when One Parent is Affected.

To discern any difference between the distributions of age of onset for those with 0 parent affected and 1 parent affected, data of all those psoriasis patients (n=304) whose exact age could be determined were examined. Results are shown as histograms, with Maximum Likelihood (ML) fits superimposed, in Figure 2a and 2b, (p180) and in Table 6 (p181). There were distinct differences in distribution when 1 parent was affected compared with 0 parents affected. When 0 parent was affected (n=225), the analysis demonstrated that a double normal distribution, with means of 22.2 years and 60.6 years for early and late onset respectively, and proportions of 2:1 and with equal variances, was the best fit ($p = 0.20$). When 1 parent was affected (n=79), a lognormal distribution gave the best fit ($p = 0.96$) with mean of 16.3 years and standard deviation of 2.2 years Table 6 (p181), indicating that most affected parents were associated with early onset. The mean onset of the patients, over all ages, when 0 parent is affected is 35.5 years which is significantly different from that when 1 parent is affected ($p < 0.01$). These

findings are different from those of Lomholt (1963) who quoted a mean age of onset when 0 parent was affected of 14.2 years and a mean age of onset of 15.7 years when 1 parent was affected, and these are not significantly different ($p = 0.33$). To examine Lomholt's data further, histograms of age of onset, when 0 parent and 1 parent were affected, were produced and the ML method applied. The results are presented in Figure 3(a) and 3(b) (p182), with ML fits superimposed. A lognormal distribution is the best fit to both histograms:- $\chi^2 = 4.34$ on 6 d.f., $p = 0.63$, and $\chi^2 = 3.26$ on 6 d.f., $p = 0.78$, respectively.

The lognormal fitted distribution in the present study, when 1 parent is affected, which is strongly skewed to the right, is indicative of a non-additive mode of inheritance operating "(phenotypic) traits governed by a multiplicative gene action tend to be skewed into an asymmetrical curve" (Stansfield, 1991). This multiplicative action, or geometric effect, occurs when the effects of individual active alleles are not independent in their action, but interact. This gives rise to a multiplicative increment increasing the contribution of the alleles above that of simply adding their contributions. Additive allelic action generally has a "normal phenotypic distribution" (Stansfield, 1991), whereas the age of onset data, in this present study, when 1 parent is affected, demonstrates that the alleles, as transmitted by the gametes, may be partly multiplicative in action.

FIGURE 2(a)

Histogram of age of onset with the fitted maximum likelihood curve when 0 parent is affected

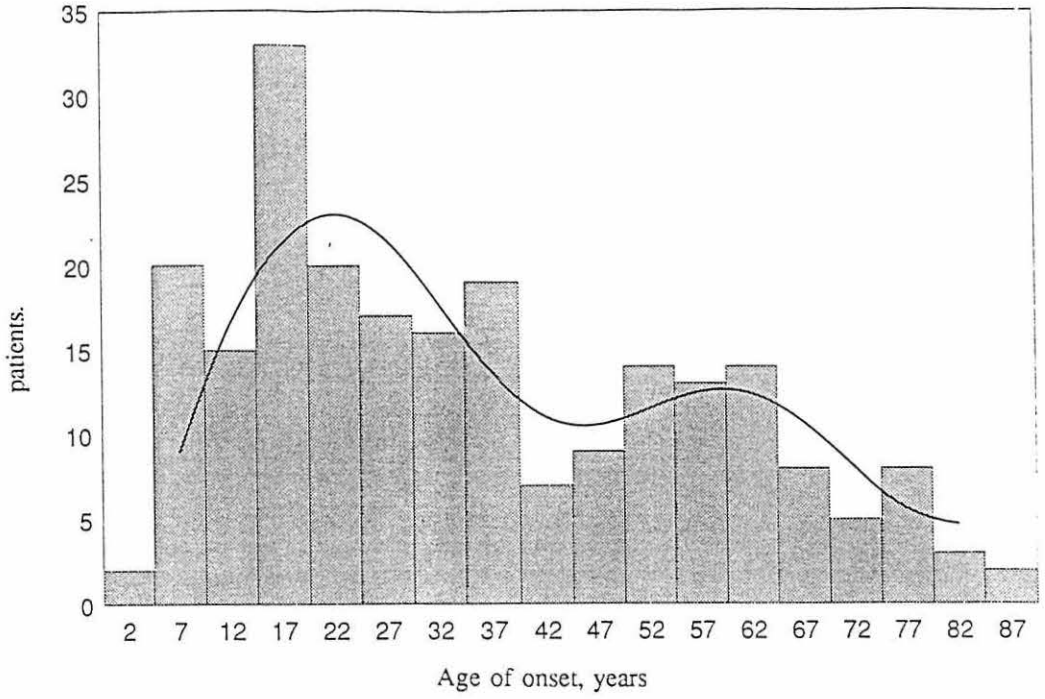


FIGURE 2(b)

Histogram of age of onset with the fitted maximum likelihood curve when 1 parent is affected

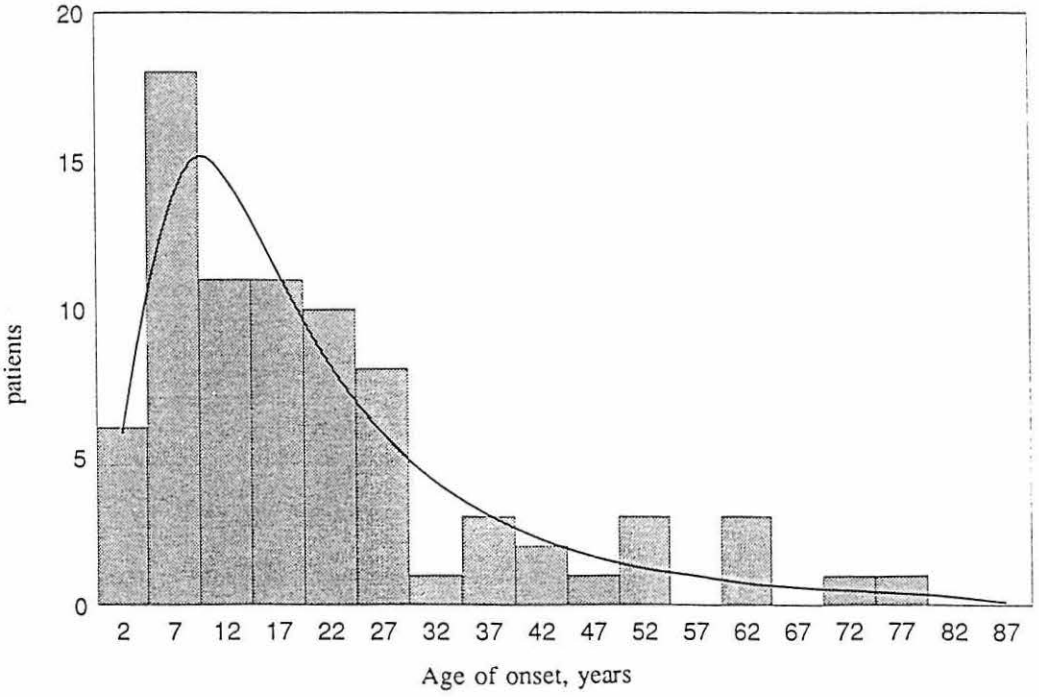


TABLE 6

The age of onset maximum likelihood fitted distributions in the patient

when 0 parent and when 1 parent are affected

		n	p	M	S.D.	95% C.I.	χ^2	df	p-value
0 parent	**Double normal model**								
	Early onset	146	0.65	22.2	12.4	(-2.10, 46.5)	14.6	11	0.203
	Late onset	79	0.35	60.6	12.4	(36.3, 84.9)			
1 parent	**Lognormal model**								
	All onsets	79	-	16.3	2.2	-	2.01	7	0.959

FIGURE 3(a)

Histogram of age of onset of Lomholt's data with fitted maximum likelihood curve when 0 parent is affected

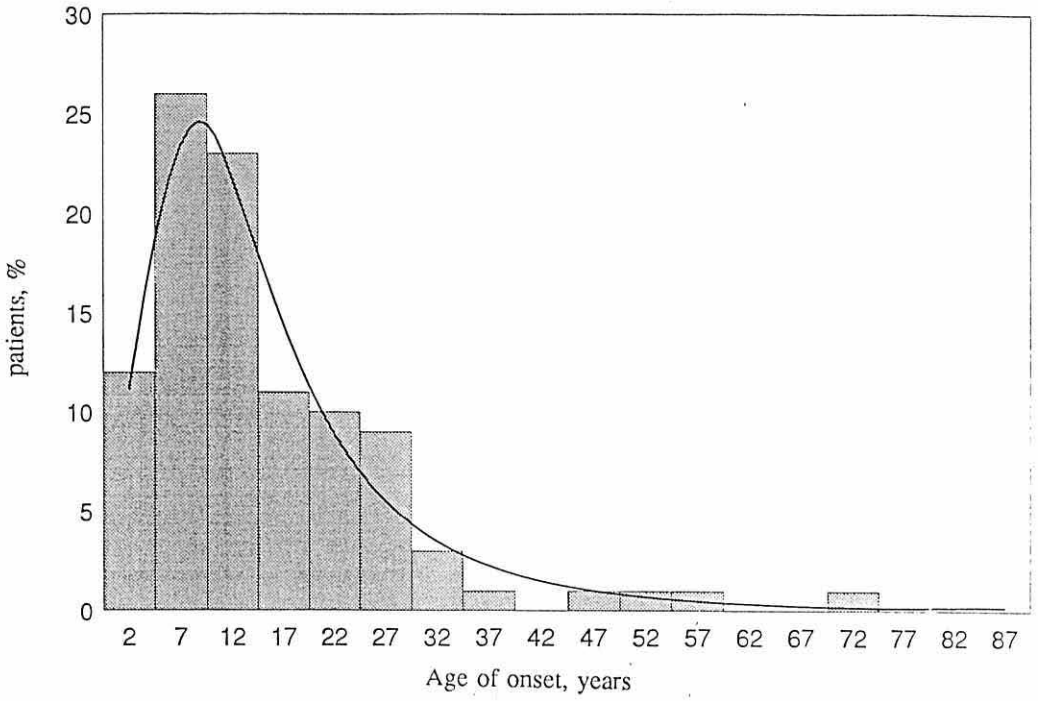
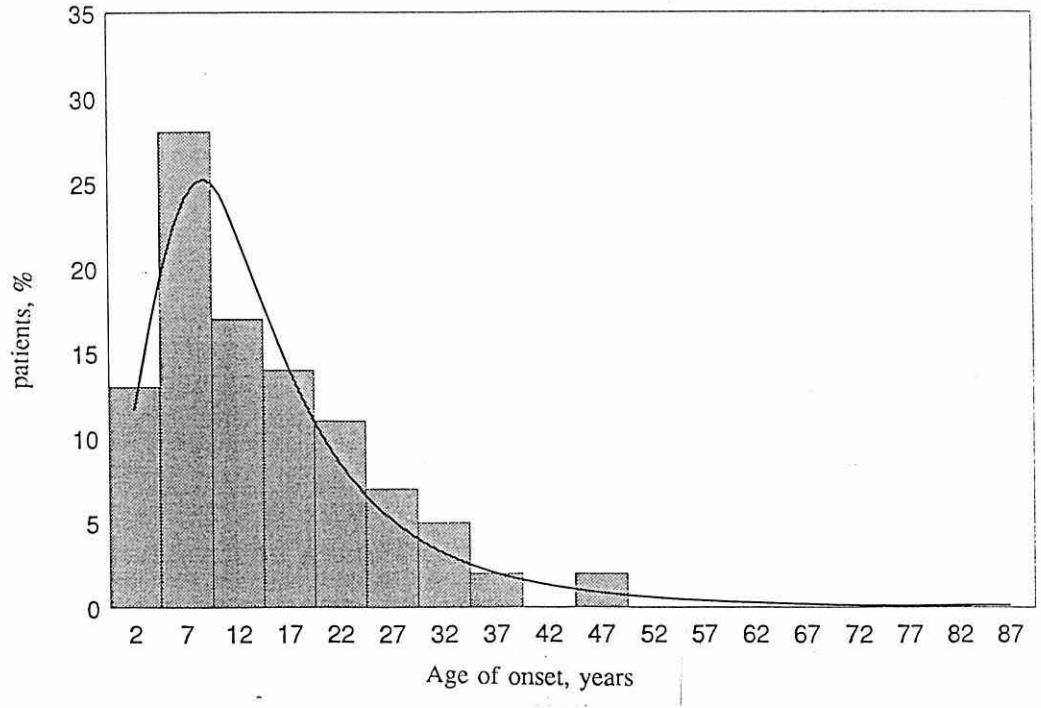


FIGURE 3(b)

Histogram of age of onset of Lomholt's data with fitted maximum likelihood curve when 1 parent is affected



These distributions when 0 parent and 1 parent are affected, can be compared with those of Nordberg - Iversen and Zachariae (1984) where the association of HLA-B13, B17 and B37 with age of onset are given. The data of these researchers indicates a strong association of these HLA antigens with early onset, where a unimodal distribution, skewed to the right with mode at approximately 15 years is demonstrated. This is very similar to the distribution when 1 parent is affected in the present study. These antigens have been reported as being in linkage disequilibrium with HLA-Cw6 (Tiilikainen et al, 1980), which has also been associated with early onset (section 5.1.2.2). This would indicate that there is an association in early onset with the B locus. Where there is a lack of association with these antigens, a bimodal distribution is shown which is similar to that shown when 0 parent is affected in the present study.

This indicates that in psoriasis patients where 1 parent is affected, the transmission of active alleles from the parent is probably in a multiplicative form, associated with the HLA-B locus and is mainly confined to early onset. When 0 parent is affected the active alleles appear to be transmitted in two different forms which are additive in their effect as indicated by the two normal age of onset distributions. Virtually all Lomholt's psoriasis probands, whether with an affected parent or not, are those of early onset, and have a similar distribution to the age of onset in the patients who have 1 affected parent in the present study, as shown in Figure 2(b)(p 180). The indication is that these probands would thus appear to be associated with the B locus, and the distribution of the second onset probands, with a lack of this association, appears to be absent in the population of the Faroes.

5.2.4 Multifactorial Inheritance

Psoriasis has not been irrefutably demonstrated to have any simple genetic inheritance and shows substantial variability in its pattern within families. However, it clearly has some hereditary basis and is widely thought to be multifactorial in inheritance. Multifactorial implies that causation of a disease results from several adverse genetic and environmental factors.

Edwards (1969) showed that for a multifactorial inheritance the frequency of the trait manifesting itself in first degree relatives of the patients, is approximately equal to the square root of the frequency in the general population. From Table 1 (p167) the prevalence of psoriasis in the relatives is 12.4% for early onset in the psoriasis patient, 6.5% for late onset and 10.1% for all onsets. The prevalence of psoriasis in the relatives of controls is 1.6%. When the results of Table 1 are compared with $\sqrt{0.016} = 0.126$ (12.6%), they are found to be reasonably close for early onset and all onsets, while late onset does not appear to be so close.

Vogel and Kruger (1967) suggested that there are three main criteria for classifying the inheritance pattern as being multifactorial:- (1) There should be many more affected siblings of patients who have a parent affected by the disease than siblings of patients who have no parent affected. This has been shown to be compatible with the data in this study (section 5.2.2). (2) A higher concordance in monozygotic twins as compared with dizygotic. There are no twins amongst the data of this present study, but Brandrup et al (1978) have shown that psoriasis demonstrates this property. (3) If the prevalence in the population indicates a sex difference, that sex which has the higher prevalence should show a higher incidence in the relatives. The data of this study indicates there are no significant differences between the sexes. There has also been consistent reporting of no sex difference in the prevalence of psoriasis.

Watson (1984) studied the family pedigrees of 698 psoriasis patients and found great variability in the inheritance pattern. He felt this supported a theory of multifactorial inheritance. He found that when 0 parent had psoriasis, then 7.8% of the psoriasis patients' siblings had psoriasis, also, when 1 parent was affected 16.4% of siblings were affected and when both parents had psoriasis 50% of siblings were affected. These findings are similar to those for over all ages of onset in this study (Table 3, p170, bottom).

5.2.4.1 Heritability theory

A method has been developed in quantitative genetics for dealing with liabilities and thresholds (see section 5.1.2.4) which can be applied to data on the incidences of psoriasis in relatives, provided the assumption of multifactorial inheritance can be made (Falconer 1965). This method attempts to quantify the relative importance of heredity and environment by comparing the variation between individuals which causes some to develop psoriasis and others not. The fraction of this variation which is attributable to genetic differences is called the genetic determination and can be defined as V_G/V_P, that is, the genetic component (G) part of the total phenotypic variance (P). The degree of genetic component can be approximated, since it cannot be measured directly in humans, by "heritabilities" which provide a good estimate of the degree of correspondence between estimated genetic values and those which can be directly measured, that is, the phenotypic values. The genetic variation is in the form of two components, additive (V_A) and non-additive (V_{NA}), so that:-

$$\text{genetic determination} = (V_A + V_{NA})/V_P$$

Heritability (h^2), as the degree of correspondence between the phenotypic manifestation and the genotype, is defined as the ratio of additive genetic variance to the total phenotypic variance, that is

$$h^2 = V_A / V_P \qquad \text{.....(1)}$$

Heritability can, therefore be equal to, or less than the genetic determination, but never greater.

Another way to express heritability is as the regression coefficient (b_{AP}) of additive genetic variance on phenotypic variance:-

$$h^2 = b_{AP}$$

These two statements of heritability are equivalent, since the phenotypic value can be subdivided up into the additive value V_A , the effect of genes individually transmitted from parent to offspring, which acts independently, and the other components. These other components are the non-additive effects (V_{NA}) of genes at different loci and the environmental influences present (V_E). The genetic components are a feature of the population from which individuals come, whilst the environmental variance is due to all the extrinsic and intrinsic influences of the conditions under which individuals live. This means that:-

$$V_P = V_A + V_{NA} + V_E$$

where $$V_{NA} = V_D + V_{EP}$$

that is the non-additive effects of dominance (D) and epistasis interaction (EP) are included with the environmental variance in the estimation of heritability.

Zero environmental variance values are only achievable with highly controlled conditions, such as in animal and plant experiments where the environmental effects on phenotypic values is minimised. In humans there tends to be some common factors in environment between relatives.

Caution is required in assuming that all diseases with a high correlation between relatives have a high genetic component, since the heritability depends on the magnitude of all the variance components including environmental

factors. Care has to be applied because, for example, tuberculosis was repeatedly found to have high heritabilities and yet the disease was controlled by antibiotics, showing that it was largely environmental (Edwards 1969). This implies that heritability may depend on the nature of the environment shared by individuals, where an environment in common, that is a reduction of V_E, will tend to increase the estimate of heritability. Also, since heritabilities measure a combination of genetic and environmental factors, as many classes of relatives should be included as possible to elucidate the effects of different environments. However, the lack of reliability of data about distant relatives can be a serious drawback. This study has data on first degree relatives only, who will share an environment to a certain extent. With psoriasis another source of variation must be included when phenotypic values are being estimated. This is due to the non - diagnosis of the condition, such as latent psoriasis, or the absence of laboratory markers for identifying potential psoriasis patients who may have a pre-psoriasis condition which never manifests itself because of lack of environmental triggers. (This may yet be at least partly resolved by identification of HLA antigens associated with psoriasis.) Lomholt (1963) has hypothesised that only about 40% of potential psoriasis patients ever manifest the condition. This was based on a study of the whole populations of certain islands in the Faroe Islands where the phenotypic expression of psoriasis would be at its highest possible because of a relatively constant environment between individuals.

The coefficient of the additive variance or the coefficient of relationship (r) is 0.5 for all first degree relatives (Galton's Law), which means that they have half their genes in common, if all the variance is additive genetic. (A heritability of 100% or an r of 0.5 can only be approximated in animal and plant breeding experiments where a completely favourable constant environment can be created.) When the environmental variance is decreased, the additive genetic variance will be a larger proportion of the total phenotypic variance and thereby heritabilities will be increased.

Heritabilities are estimated from the prevalence of the condition in the relatives of those affected, compared with the prevalence in either the population or the relatives of some suitable controls. Controls were used in this study and the assumption was made, for calculation purposes, that the liability in the relatives are normally distributed. This is actually in error as the manifestation of psoriasis is in the upper tail of the normal liability distribution and in itself cannot be normally distributed, nor its manifestation in associated relatives. However, Falconer (1965) states that animal experiments have repeatedly shown that the error is so small as to be safely disregarded, since it has been demonstrated that the distribution in first degree relatives is not significantly different from normal.

Falconer (1965) gives models for the evaluation of heritabilities based on whether prevalences for comparison with affected relatives are from the general population or from controls. His method 2 was chosen because this study has data from controls and, since only first degree relatives were used, $b = rh^2$ where $r = 0.5$ as before. This means that heritability with regard to liability was twice the coefficient of the regression of relatives on patients, that is, $h^2 = 2b$. (Falconer uses the term "incidence" to mean the "prevalence" of the condition when defining the percentage of affected relatives.)

5.2.4.2 Computing heritabilities

The evaluation of mean liability to psoriasis is made by referring to tables of the normal distribution. The prevalence in the relatives (q) gives the normal deviate x (in standard deviation units) of the threshold from the mean. This is carried out for both psoriasis patients' relatives and controls' relatives.

The mean liability in relatives of psoriasis patients differs from that of the controls relatives by the amount a in standard deviation units. The ratio of the two differences in mean liability can be expressed as the regression of relatives on patients and controls.

A programme for use with the statistical package Minitab on the VAXA mainframe was written to calculate 4 distinct values for each individual measurement. This programme is given in the Appendix to this Chapter. These values were:-

(1) The regression coefficient **b**, prevalence in relatives on the prevalence in the patients, is given by

$$b = \frac{p_c\,(x_c - x_r)}{a_c}$$

p = 1-q, where q is appropriate prevalence, that is, affected individuals/total individuals. **x** = standard deviations of the mean liability to psoriasis, from the threshold, of the group. **a** = mean deviation of those with psoriasis from the control population mean. Subscript **c** = relatives of controls, subscript **r** = relatives of patients.

(2) The variance of the estimated regression coefficient $\mathbf{V_b}$, where :-

$$V_b = \left[\frac{p}{a} - b\,(a' - x)\right]^2_c W_c + \left(\frac{p}{a}\right)^2_c W_r$$

subscripts c and r are as before.

p, x, a and q are as before

W = $p/(a^2A)$ where A is the number of affected individuals in the group

a′= $a\{(p-q)/p\}$ for controls

(3) The standard error, equivalent to twice the square root of V_b above, as a percentage.

(4) The heritability, in this case twice the regression coefficient b, since first degree relatives were used, and presented as a percentage.

Minitab procedures already exist for calculating the values of x in standard deviations and a, the standard normal ordinate at the "incidence" q%, which was equivalent to using the tables of Appendix A of Falconer (1967).

5.2.4.3 Heritability Results

Results for the groups in this study are given in Table 7 (p192), where the heritabilities are for total first degree relatives. Using the test statistic:-

$$\frac{h_1^2 - h_2^2}{\sqrt{(S.E._1)^2+(S.E._2)^2}}$$

under the assumption that it is approximately normally distributed for large samples, a significant difference is found between the heritabilities of early onset (74.9%) and late onset (52.7%) ($p < 0.05$), which implies a higher additive genetic component in the early onset groups compared to the late onset groups. Estimates of heritabilities at 10 year intervals were attempted but, because of lack of numbers of affected relatives in the control group, some categories could not be computed as they contained zero values.

Generally, small differences in the heritability estimates between male and female are difficult to interpret because of the large standard errors involved. Over all ages of onset the heritabilities for males and females are similar (71.3% and 69.7% respectively), which accords with other studies where there has been no difference in the prevalence in the relatives, between sexes, when taken as one single distribution over all ages (Watson et al, 1972; Ananthakrishnan et al, 1973;1974).

However, a lower heritability (using all relatives) in females in late onset, compared with males (49.4 $\pm$ 11.2% and 59.5 $\pm$ 13.8% respectively), may indicate the influence of the menopause as an environmental factor.

Heritabilities for different types of first degree relatives were also calculated for the early onset group and the late onset group (Tables 8, p193 and 9, p194, not divided up by sex).

Table 8 (early onset) (p193) shows that heritability when siblings are considered is quite high at 89.1% but this has to be treated with care as only 2 siblings with psoriasis were reported for the control group and the standard error is 11.5% . The most appropriate estimate of heritabilities would normally be from the numbers of affected siblings of psoriasis patients and controls, because they are approximately the same age. The result for parents is similar to the heritability for total relatives in the early onset group. The children demonstrate a much lower heritability of 52.8% and the reason for this may be that all potential psoriasis patients in the children have not reached the age at which the disease will be manifested, since their parents are all early onset psoriasis patients.

With the late onset group (Table 9, p194) the heritabilities for parents are higher than those for siblings (49.2% and 40.3% respectively), whereas the children demonstrate a high heritability of 72.8%, but with a high standard error of 15.4% due to low numbers. The parents of this group are more likely to have had a lifespan in which to manifest psoriasis, while siblings may yet do so.

Treating children as a confounding factor, and using parents and siblings only, produces heritabilities of 79.8 $\pm$ 7.4 % in early onset and 44.3 $\pm$ 10.5 % in late onset for the two sexes combined.

Tables 10 (p195) to 13 (p198) are equivalent to Table 8 and 9, but divided up by sex. Here, where there is zero psoriasis in the relatives in some control categories, h^2 cannot be calculated as the q (incidence) is zero and neither the x in s.d.'s nor the a can be calculated. This limits interpretation and low numbers elsewhere, especially in the relatives of controls, make the results less reliable. However, parental h^2 is the same for both sexes in early onset, 80.0% for males, 80.1% for females. For the total relatives h^2 is approximately the same in both sexes (h^2 = 77.5% for males, 79.1% for females) for early onset. These are not significantly different (p = 0.46).

TABLE 7

Heritabilities of psoriasis, using all first degree relatives, for males and females, and early onset and late onset

	Psoriasis Proband n = 413		Controls Proband n = 283		
Age of onset	**Aff. relative**	**Total relative**	**Aff. relative**	**Total relative**	**$h^2 \pm$ S.E. %**
<40 Male	66	661	2	199	77.5 ± 14.2
<40 Female	119	826	13	619	79.1 ± 7.8
<40 Total	185	1487	15	818	74.9 ± 6.8
≥40 Male	27	434	3	312	59.5 ± 13.8
≥40 Female	35	522	8	473	49.4 ± 11.2
≥40 Total	62	956	11	785	52.7 ± 8.6
All Males	93	1095	5	511	71.3 ± 9.5
All Females	154	1348	21	1092	69.7 ± 6.3
Total	247	2443	26	1603	68.1 ± 5.2

TABLE 8

Heritabilities of psoriasis for the 3 types of first degree relatives, and both sexes combined at early onset.

	Psoriasis Proband n = 267		Controls Proband n = 161		
Early onset both sexes	**Aff. relative**	**Total relative**	**Aff. relative**	**Total relative**	**$h^2 \pm$ S.E. %**
Parents	87	534	9	322	78.7 ± 10.2
Siblings	71	675	2	349	89.1 ± 11.5
Children	27	278	4	147	52.8 ± 17.0
Totals	185	1487	15	818	74.9 ± 6.8
Totals, no children	158	1209	11	671	79.8 ± 7.4

TABLE 9

Heritabilities of psoriasis for the 3 types of first degree relatives, and both sexes combined at late onset.

	Psoriasis Proband n = 146		Controls Proband n = 122		
Late onset both sexes	**Aff. relative**	**Total relative**	**Aff. relative**	**Total relative**	**$h^2 \pm$ S.E. %**
Parents	19	291	4	244	49.2 ± 15.5
Siblings	20	393	5	316	40.3 ± 14.4
Children	23	272	2	225	72.9 ± 15.4
Totals	62	956	11	785	52.7 ± 8.7
Totals, no children	39	684	9	560	44.3 ± 10.5

TABLE 10

Heritabilities of psoriasis for the 3 types of first degree relatives, males, early onset.

	Psoriasis Proband n = 122		Controls Proband n = 44		
Early onset males.	**Aff. relative**	**Total relative**	**Aff. relative**	**Total relative**	**$h^2 \pm$ S.E. %**
Parents	37	244	2	88	80.0 $\pm$ 18.6
Siblings	25	312	0	85	-
Children	4	105	0	26	-
Totals	66	661	2	199	77.5 $\pm$ 14.2
Totals, no children	62	556	2	173	79.6 $\pm$ 14.6

TABLE 11

Heritabilities of psoriasis for the 3 types of first degree relatives, males, late onset.

	Psoriasis Proband n = 69		Controls Proband n = 52		
Late onset males.	**Aff. relative**	**Total relative**	**Aff. relative**	**Total relative**	**$h^2 \pm$ S.E. %**
Parents	8	137	0	104	-
Siblings	11	172	2	119	47.7 ± 21.6
Children	8	125	1	89	57.3 ± 25.4
Totals	27	434	3	312	59.4 ± 13.8
Totals, no children	19	309	2	223	60.5 ± 16.5

TABLE 12

Heritabilities of psoriasis for the 3 types of first degree relatives, females, early onset.

	Psoriasis Proband n = 145		Controls Proband n = 117		
Early onset females.	**Aff. relative**	**Total relative**	**Aff. relative**	**Total relative**	**$h^2 \pm$ S.E. %**
Parents	50	290	7	234	80.1 $\pm$ 12.4
Siblings	46	363	2	264	92.6 $\pm$ 12.6
Children	23	173	4	121	62.9 $\pm$ 18.1
Totals	119	826	13	619	79.1 $\pm$ 7.8
Totals, no children	96	653	9	498	83.6 $\pm$ 8.7

TABLE 13

Heritabilities of psoriasis for the 3 types of first degree relatives, females, late onset.

	Psoriasis Proband n = 77		Controls Proband n = 70		
Late onset females.	**Aff. relative**	**Total relative**	**Aff. relative**	**Total relative**	**$h^2 \pm$ S.E. %**
Parents	11	154	4	140	37.1 ± 20.5
Siblings	9	221	3	197	33.4 ± 19.4
Children	15	147	1	136	83.9 ± 19.4
Totals	35	522	8	473	49.4 ± 11.2
Totals, no children	20	375	7	337	34.6 ± 14.0

For late onset the equivalent figures are 59.4%% for males and 49.4%% for females. These late onset heritabilities are not significantly different ($p = 0.29$). The tables show that, in early onset, 13.3% of children of affected females have psoriasis, compared with 3.8% of children of affected males. The equivalent figures for late onset are 10.2% (children of affected females) and 6.4% (children of affected males). This is not in accordance with some other studies where a higher percentages of affected children are reported to have been born to male psoriasis patient compared with females (Happle, 1993).

The heritabilities show an overall decrease with increasing age. Falconer (1967) gives a model of variability (Model II) which suggests that if there is an increase in variability which manifests itself as a decrease in heritability with increasing age, then it is probable that the source of variation is environmental.

We may conclude from these results that a heritability of 79.8% at early onset (Table 8, p198, with children excluded) indicates a strong additive genetic component in the inheritance of psoriasis with non-additive genetic component and environmental factors playing a minor role. While at late onset, $h^2 = 44.3\%$ (Table 9, p144, with children excluded) and this suggests that the role of the non-additive genetic component and the environment play a more important part in the manifestation of the disease.

5.2.5 Genetic Correlations and the Influence of Liability at Different Ages by Different Genes.

The genetic correlation ($\mathbf{r_G}$) between affected groups is the degree of correlation expressing the extent to which these groups are influenced by the same genes, or the correlation of "breeding values". Its estimation is analogous to the estimation of heritability and generally:-

$$\mathbf{b = rh_1h_2r_G}$$

where $\mathbf{r}$ is 0.5 for first degree relatives, as before, $\mathbf{h_1}$ and $\mathbf{h_2}$ are the square roots of the heritabilities of group 1 and group 2 respectively (Falconer, 1965).

As with heritabilities, the regression (b) in respect of liability between relatives generally can be obtained by the formula $b = (x_c - x_r)/a_c$ where x_c is the liability in the relatives of controls, x_r is the liability in the relatives of the patients and a_c is the average deviation in liability of the patients from the mean in the controls. If the patients and the controls can be divided into two groups, for example, male and female or <40 years and ≥40 years, then the general formula for estimating genetic correlations will be:-

$$rh_1h_2r_G = \frac{x_{c2} - x_{r2}}{a_{c1}}$$

This replacement of the mean of the liability in the controls of one group, by the mean of the liability in the controls of the other group effectively gives a weighted regression co-efficient and enables r_G to be calculated. If this estimate of $\mathbf{r}_G$ is approximately 1, then the same set of genes probably control the liability to the condition. If $\mathbf{r}_G$ is not equal to one, then it is generally indicative of two sets of genes operating. However, it can also indicate the same set of genes, but acting at different ages. For example, if $\mathbf{r}_G$ between liability at different ages is <1, then both of these situations could apply.

5.2.5.1 Estimates of genetic correlation

The heritabilities of psoriasis for males and females in this study were found to be similar, therefore the data for the two sexes were combined and used in the estimation of the genetic correlation between early and late onset divided at the age of 40 years. The children of probands were excluded because they could be a confounding factor between the early and late onset in that the early probands may not be of an age to have had children, since the average age at the time of examination was 41 years, that is, 9 years greater than the age of onset (Chapter 4, Table 1). If parents plus siblings of the controls of the late onset group are used, with the parents plus siblings of the psoriasis patients of the early onset group, then $\mathbf{h_1h_2r_G}$ can be obtained, using the above formula which gives a weighted regression coefficient.

The results of heritability estimation for total relatives minus children (Table 8, p193 and Table 9, p194) are 79.8±7.4% for early onset and 44.3±10.5% for late onset. This gives an estimate of $r_G = 0.75$ using the above formula. This result is <1 and gives an indication that there could be different genes operating between early and late onset.

5.2.5.2 Variability due to age

A change in environmental variance or a change in mean liability may account, both individually or together, for a change in heritability.

Falconer (1967) suggests that the mean liability for different age groups can be used to provide the degree of change in genetic variance; by expressing the variance in terms of genetic rather than phenotypic values. The mean liability in phenotypic values (x) divided by the square root of the heritability (h), for each age group, gives the mean liability (m) in units of genetic standard deviation:-

$$x / h = m / s.d._G$$

Any change in this value would indicate a change in mean liability or a change in genetic standard deviations, since m is the mean number of units below the threshold. However, if this value does not differ between groups, it means that neither the mean liability nor the genetic variance has altered and any change is due to environmental influences.

The results of this study are given in Table 14 (p202), with different dividing points between early and late onset. This shows consistently that there is an increased mean liability as age of onset increases.

If the mean liability remains constant, then any change in the heritability would be due mostly to environmental factors. However, the mean liability in both phenotypic and genetic standard deviations increases, so not all of the change in heritability is due to environmental factors. In other words, there is an increased genetic liability operating with increased age. This increased genetic liability between early and late onset indicates different genes,

TABLE 14

Mean liability to psoriasis with 5 year dividing points between early and late onset, using parents and sibling data combined

Onset cut point (years)	q%	x	x/h
20	15.5	1.015	0.108
25	15.3	1.024	0.109
30	15.3	1.024	0.105
35	14.1	1.076	0.120
40	13.1	1.122	0.126
45	12.6	1.146	0.133
50	12.3	1.160	0.134
55	12.3	1.160	0.135
60	11.7	1.190	0.142

or a different mixture of genes being present, or that the same set of genes is present but with individual genes varying in their time of action (Falconer 1967).

5.2.6 Discussion of Results of Heritabilities and Genetic Correlations

The marked differences throughout in heritabilities between early onset and late onset psoriasis would indicate two distinct modes of inheritance. From this model both would be expected to be polygenic, but because of the consistent difference between the two onsets when examining liabilities with regards to different relatives, they would vary in their non-additive genetic and environmental components.

As before:- $h^2 = V_A/V_P = V_A/(V_A + V_{NA} + V_E)$

and from Table 8 (p193) for early onset :- $0.80 = V_A/V_P$ when children are excluded.

Thus the additive genetic variance accounts for 4/5 of the phenotypic variability in early onset. This indicates that the earlier onset is predominantly a result of the additive affect of genes as transmitted from parent to offspring, with non-additive genetic effects plus environmental factors playing a lesser role.

Similarly from Table 9 (p194), in late onset, $0.44 = V_A/V_P$ when children are excluded, that is, the additive genetic variance accounts for less than 1/2 of the total phenotypic variability and so the additive genetic component is approximately equal in effect to the non-additive genetic and environmental factors combined. More evidence for the influence of environment comes from comparing the results of the heritability estimates for parents and siblings in both early and late onset. Table 8 (p193) indicates a higher heritability for siblings, for early onset in the patient, who would share an environment to a larger degree, than for parents. Conversely, for late onset (Table 9, p194) a higher heritability is indicated for parents rather than siblings,

suggesting that a common environment plays a lesser role, and that there is a greater environmental variation in the siblings in late onset. There appears to be an enhancement in the influence of the environment in the results for females of late onset. Table 13 (p198) gives results for females of late onset which demonstrates that the heritability in the siblings is 33.4 $\pm$ 19.4%. This is compared with the equivalent results for males (Table 11, p196) of 47.7 $\pm$ 21.6%. Large standard errors are involved, but these results suggest that it is possible that female psoriasis patients are more influenced by environmental factors, for example, the menopause, at late onsets. The conclusion from these results could be that an uncomplicated polygenic role is operating in early onset while in late onset the polygenic factors are more complex with interaction between the genes and also interaction between the genes and the environment involved. It may also indicate that the assumed smaller environmental component, in early onset means that psoriasis is more sensitive to environmental triggers.

As demonstrated in section 5.2.5.2., there is an increase in the genetic liability with age which could indicate the same set of genes differing in their time of action. However, the genetic correlation between early and late onset indicates that there are two distinct genotypes with possible separation at the age of 40 years. There is a possible minimum at the age of 30 years, but low numbers in the controls are involved here and this requires further elucidation in some future work.

This separation at the age of 40 years, into early and late onsets, is used because of the expression of the phenotype, based on the distribution of age of onset, as reported in Chapter 4. The latent period in psoriasis is unknown, but, for example, Burch and Rowell (1965), suggested that it may be 5 years. Also unknown is the time between manifestation of the first symptoms of the condition and the diagnosis, so a delay of several years is possible between the assumed genotype separation and phenotypic expression of this separation of the two onset groups in psoriasis.

APPENDIX

Programme for calculating heritabilities

```
let k1=A (ps patients)
note aff. rels of ps patients
let k2=N (ps patients)
note total rels of ps patients
let k11=A (cont)
note aff. rels of controls
let k12=N (cont)
note total rels of controls
exec 'herit.mtb'
let k3=k1/k2
note this is q of ps patients
let k4=1-k3
note this is p of ps patients
let k5=k3*100
print k1-k4
print k5
note this is q% of ps patients
invcd k4 k3 k6 k7;
normal 0 1.
pdf k6 k8.
let k7=k8/k3
print k6 k7
note this is x and a for pspatients' relatives
let k13=k11/k12
note this is q for cont
let k14=1-k13
note this is p for cont
let k15=k13*100
print k11-k14
print k15
note this is q% of cont
invcdf k14 k13 k16 k17;
normal 0 1.
pdf k16 k18.
let k17=k18/k13
print k16 k17
note this is x and a for controls' relatives
let k21=k17((k14-k13)/k14)
note this is a dash
let k22=k4/((k7**2)*k1)
note this is W rel  (of Ps patients)
let k23=k14/((k17**2)*k11)
note this is W cont
let k30=(k14*(k16-k6))/k17
note this is b
print k21 k22 k23 k30
let k31=(((k14/k17-k30(k21-k16))**2)*k23)+((k14/(k17**2))*k22)
let k32=(sqrt k31)*200
print k30
note this is b
print k31
note this is Vb
print k32
note this is S.E.%
let k33=k30*200
print k33
end
save 'herit.mtw'
nojournal
```

CHAPTER 6

DISCUSSION, CONCLUSIONS AND SUGGESTIONS FOR FURTHER WORK

6.1 Introduction

The main results of this study in relation to the concomitance of psoriasis and AD, the age of onset and also the genetics of psoriasis are highlighted in this chapter. These are discussed and related to current research. Conclusions are then drawn and suggestions for further research made. The publications associated with this study are listed, and copies of these included at the back of the thesis.

6.2 Concomitance of psoriasis and AD

6.2.1 Background to the Research

The original study arose from the observation that there was a not infrequent co-occurrence, in clinics in Gwynedd, of psoriasis in AD patients and vice-versa. This was contrary to that generally believed and taught. Notably, Christophers and Henseler (1987) stated that psoriasis and AD were mutually exclusive and they suggested that opposing pathomechanisms may be responsible for this.

A study was initiated to examine patients who came to dermatology clinics in Gwynedd, specifically for the presence of psoriasis in AD patients and vice versa and for the two conditions in controls. The main aim was to establish whether the two diseases co-existed in patients or not. Only those patients with unequivocal evidence of either condition were included as probands, whilst others, with no evidence of inflammatory dermatoses were used as controls.

6.2.2 The Main Results

The basic findings, of 9.5% of psoriasis patients having AD and 16.7% of AD patients having psoriasis, either concurrently or consecutively, are clear evidence of concomitance. They are backed up by family history of the two conditions (section 3.1.5) and all the detailed clinical examination listing the features recorded in each patient. The results show that the two conditions co-exist more frequently than generally believed by dermatologists.

The demographic details of all the patients (section 3.1.3) indicate that the patients were not unusual in ages, onset and pattern of the disease categorisation. The male to female ratio in this study was 1:1.3 , also similar to that found by others (section 3.1.1) reflecting the hypothesis that women tend to seek diagnosis and treatment for skin problems more frequently than men.

A prevalence of 1.8% for psoriasis was estimated from the clinic controls (section 3.1.5.4.) and this is similar to other recent estimates, for example Elder et al (1994) stated that there is a prevalence of about 2% in the U.S.A. A study of twins has indicated a cumulative prevalence of between 1.6% and 2.1% in 30 to 60 year olds in Australia, where British ancestry is common. (Duffy et al, 1993).

This study found that 40% of psoriasis patients had at least one first degree relative with psoriasis and this agrees with the family incidences of most studies published to date (section 3.1.1).

The prevalence of AD in this study was estimated to be 3.5% from the clinic controls (section 3.1.5.4). The prevalences reported by Williams (1994) are similar for social classes I, II and III non-manual, but the two studies cannot be directly compared as William's percentages are point prevalences, whereas the estimate of this study was the accumulated prevalences to date at the time of examination. However, there may well be different prevalences in different geographical areas, even within Britain, and the prevalence in the population is reported to be increasing (section 1.4.4). The environment is known to play a large role in the aetiology of AD (section 1.4.6).

The prevalence of a history of AD in the families of AD patients in this study, where at least one family member had AD, is 50% (section 3.1.5). Furthermore, 40% of the AD patients' relatives had asthma and 41% had hay fever. In the patients themselves, 48% had asthma and 40% had hay fever, which is similar to the findings of others (Küster et al, 1990).

Given these estimates for the prevalence of psoriasis and AD, the genetic predisposition to both will be co-inherited occasionally (section 3.2.3). This genetic predisposition is demonstrated in Chapter 3, Figure 2, where the family histories show close matching of the group with dual pathology to the family histories of both the "pure" psoriasis and "pure" AD groups. However, the results have demonstrated that the frequency of the concomitance is greater than that which would occur by chance (section 3.2.2). Chapter 3, Figure 3 hypothesises that those with one condition have an enhanced susceptibility to the other because the immune system is already disturbed and common pathomechanisms may facilitate the expression of the other condition. There may also be, in the immunological process, factors such as "quiet" minor genes being activated and thus promoting expression of a latent psoriasis or a latent AD condition. It is also possible, though there is no real evidence for this since only the phenotypes are being measured, that there could be some co-segregation of the gene loci in the population studied.

6.2.2.1 The clinical features

The features recorded in the clinical examination (section 3.3) are consistent with those generally regarded as characteristic for psoriasis and for AD individually (Chapter 2, Appendix B).

Of particular interest is the position of the group of patients with both conditions in relation to the clinical features. Chapter 3, Table 9 gives the impression that there is suppression of the features which are deemed to be "markers" for psoriasis or "markers" for AD in this group. For example, the frequencies in the group with psoriasis plus AD of lichenification, generalised severe itch, Dennie Morgan folds, asthma, hay fever, whole skin itch,

xeroderma, animal hair intolerance and IgE >80ku/l (all generally considered to be features of AD), lie between the frequencies found in AD and those found in psoriasis. Of the features generally considered to be psoriatic, the group with psoriasis plus AD show these features less commonly than the "pure" psoriasis group.

The indication is that there is less evidence of AD features in the presence of psoriasis; also, features of psoriasis are occurring less frequently in the presence of AD. This may indicate that there is a modification of the clinical features of each condition in the presence of the other, a finding believed to be unreported in the literature as yet. This concurs with the statement that no patient was seen with both severe psoriasis and severe AD **concurrently** (Beer et al, 1992).

The suggestion made in this study is that the clinical course of the two diseases may not be independent of each other, but be affected by common factors that promote the triggering of the other, and, when both are manifest together, some moderation of the clinical features of the other condition appears to occur. Fartasch et al (1989) suggest that AD has a suppressive influence on keratinization indicating that the hyper-keratinization process of psoriasis would be reduced.

6.2.3 Why does the Present Study Conflict with Some Other Studies?

The present study scrutinised the possibility of the co-existence of psoriasis and AD by carrying out a deliberate search for the presence of the two conditions in every psoriasis and AD patient as well as in the controls, who presented at the dermatology clinics in Gwynedd. Because the population of the area is relatively static, and also because some of the patients have been followed up for 25 years by one dermatologist, the patients' history and the family history could be accurately documented. This meant that, in contrast to previous studies, both the concurrent and the consecutive occurrences of psoriasis and AD could be clearly ascertained and the prevalence of psoriasis

and atopy in families determined. As might be anticipated from the typical age of manifestation of psoriasis and AD, psoriasis generally followed AD in consecutive occurrences, however, the ratio of concurrent to consecutive incidences was 3:1.

As well as looking for AD in psoriasis patients, this study examined for the presence of psoriasis in AD patients, rather than atopy in psoriasis patients, as has been carried out in previous studies (Christopher and Henseler, 1987). The prevalence of 16.7% of psoriasis in AD patients, is much higher than expected.

There are methodological differences between the present study and other studies. For example, the research of Christophers and Henseler (1987) was a retrospective study from hospitalised patients' records and thus not a deliberate prospective search for the two conditions, as this study was. These researchers did not record the consecutive occurrence of psoriasis and AD. The coexistence between psoriasis and AD has been further disputed by Henseler et al (1992), who have found that in psoriasis in-patients at a hospital in Kiel, Germany, there was less AD and asthma recorded than in other patients, but their study has the same methodology as the previous study.

It is possible that when psoriasis is very mild, it may be being overlooked when AD is severe and extensive. Happle (1993) stated, that there are various gradations in skin conditions, which prompted the question of when it should be called psoriasis. Those whose assumption is of the mutual exclusivity of psoriasis and AD may well be missing mild psoriasis in AD patients, particularly in children, where psoriasis is considered to be uncommon before puberty. For example, a small patch of psoriasis on the back of the scalp could be overlooked in the presence of severe AD in childhood unless both conditions were being deliberately sought. The difference in the typical age at which the conditions occur means that the likelihood of finding concurrent lesions is small, less than 0.01% of the population on average (Röcken et al, 1991). Psoriasis may be superimposed on flexural AD, and

AD may be present in areas of psoriasis, sometimes called eczematous psoriasis (Epstein and Maibach, 1991).

Another reason for missing the dual pathology is the reluctance, especially in a busy clinical department, to assign two diagnoses to a patient. There can also be introduction of subjective differences in approach to diagnosis and methods of recording this, with several dermatologists involved rather than just one.

6.2.4 Recent Corroborative Evidence

It is possible that there are differences in different populations, where the genetic profile of the population would influence the possibility of co-existence of the predisposition to psoriasis and AD. However, the population in Germany studied by Christophers and Henseler (1987) is unlikely to be that which excludes their co-existence because Röcken et al (1991) have examined, thoroughly, sixty eight psoriasis patients in a clinic in Munich for the presence of atopic disease. They found that eight of these (11.8%) had AD. They stated that this was the same prevalence as in the local population and concluded that there was not mutual exclusiveness.

Further evidence to support the findings of the present study comes from the recent research by Williams and Strachan (1994), using the data of the National Child Development Study (Shepherd, 1985) on all children who had been born in Britain between March 3rd - 9th, 1958. In a follow up of 354 children who had eczema at the ages of 11 years and/or 16 years, 5 children who had visible eczema were found to have concomitant psoriasis. This represented 1.4% of eczema patients and a relative risk of 1.4 of psoriasis in these patients, compared with controls. The relative frequency of atopic eczema to other forms of eczema was stated, from the authors' previous research to be 50 fold, indicating that the vast majority of the patients were atopic. They state that "psoriasis may co-occur concurrently and consecutively in the same individuals" and concluded that "there is little evidence to support

the notion that psoriasis and atopic eczema are two mutually exclusive diseases".

6.2.5 Final Comments on Concomitance of Psoriasis and AD

Attitudes may be changing towards the concomitance of psoriasis and AD. The statements of Garofalo et al (1989) (section 3.2.6.2) certainly indicate this. J.D. Bernard (1993) commented on a report of the first part of this study (Beer et al, 1991) on the basic results on concomitance, that "not only do they occur together, they can make each other worse". This was borne out by an example in Chapter 3, Table 4, where underlying flexural eczema, in a patient with a strong family history of atopy, only became apparent when the patient was treated with topical cortico-steroids, all other psoriasis therapy having failed (section 3.2.4).

Patients with psoriasis unresponsive to conventional therapies should be suspected as possibly having latent AD, especially if there is a family history of atopy. Generally, atopics with eczema affecting elbows and knees are not easy to treat; perhaps there is latent psoriasis on these sites. Since psoriasis and AD both share some immunological defects (Chapter 1, Appendix), should it be surprising if they are found concomitantly? Perfetti et al (1991) indicated an association between atopy and vitiligo, whilst an association between psoriasis and vitiligo had previously been shown by Menter et al (1989) and thought to be due to common immunological alterations.

The main conclusion is that psoriasis and AD are not mutually exclusive. Furthermore, this study suggests some mutual influence when the conditions co-exist.

6.3 **The age of onset in psoriasis**

The suggestion had been made that there are two types of psoriasis, distinguished by age of onset and familial association (Henseler and Christophers, 1985). A preliminary examination of the data on onset in the psoriasis patients indicated that there may indeed be two distinct age of onset

distributions (Chapter 4, Appendix). Mathematical models were applied to identify these. Subsequently, a comparison with other epidemiological studies was sought by accumulating ages of onset and correcting for survival rates to produce an expected age profile of those with psoriasis in the population.

6.3.1 The Results of Age of Onset

The finding of this study (section 4.3), by the method of maximum likelihood (Ross, 1980), is that there are two ages of onset in psoriasis where someone whose onset is <40 years is more likely to be early onset, while someone with onset >40 years is likely to be late onset. This had not been previously shown in the U.K. It was substantiated by using two sets of data from two geographical locations in the U.K. and by using both prospective and retrospective data. The onsets of the phenotypic expression of psoriasis involve some delay due to a latent period after the triggering of the condition and also to the interval between manifestation of first symptoms and diagnosis.

An analysis of the psoriasis patients' ages at the time of examination was undertaken, to see if this biased the onset results. The age distribution, rather than being a confounding factor of the onset distributions, is a function of the onsets and reflects the referral pattern of the patients from their G.P.s to dermatology clinics in the U.K. (section 4.5). When a formula for survival rates (section 4.5.1) was developed and applied, this resulted in a distribution of expected ages of those with psoriasis in the population which was similar to those found in other epidemiological studies, for example, Farber and Nall (1974).

This study, for the first time, gave a distribution of prevalence of history of psoriasis in the relatives, which was associated with the age of onset in the patients (Chapter 4, Table 12). Factors were developed to correct for the difference between the onset and the age of the patient at the time of examination, when more relatives could have been accumulated as the patient gets older. Formal analysis of this distribution demonstrated the presence of two negative binomial distributions (section 4.6) which inferred strongly that

there are two quite distinct onsets in psoriasis, showing increased familial association with both the earlier onset class in the early onset distribution and the earlier onset class in the late distribution (section 4.6.4). It thus fits in with the accepted idea that the earlier the onset, the greater the familial association in psoriasis but for both early and late onset groups separately. It also indicates that early onset and late onset are probably genetically controlled, as opposed to the late onset being sporadic and without familial association as stated by Henseler and Christophers.

6.3.2. Comparison with Research Which has Not Demonstrated Bimodality

Lomholt (1963), in the Faroes, found that 96.4% of psoriasis patients examined had an onset of <40 years. The equivalent in the present study is 69% (from Chapter 4, Table 2), indicating that fewer patients in the present study had early onset compared with the Faroese population. Swanbeck et al (1994) in a study in Sweden, found that 90% of psoriasis patients had an onset before the age of 50 years. (The equivalent figure for this study is 74%, Chapter 3, Table 2.) They did not find a bimodal distribution for males. However, they found a peak in the age of onset distribution for females, demonstrated in a graph in their paper at the age of 50 years, but explained this as being entirely due to the menopause. The onset distributions in this present study showed that there is a second onset for males as well as females.

An absence of two ages of onset in psoriasis is being reported elsewhere. For example Park et al (1992) in a study in Korea, found that 80% of their psoriasis patients had an onset of < 40 years. Traupe et al (1992) drew conclusions on the relationship between the sex of the affected parents and the birth weight of their children, generalised to all patients regardless of onset, while ignoring that the majority of fathers and mothers would have been below 40 years of age when the child was born, and therefore be of early onset

psoriasis. Further evidence for the non-recognition of two distinct ages of onset has been shown in a review article by Elder et al (1994) who suggest that it is a reasonable strategy that all genetic analysis and investigation into candidate genes should be done on people with juvenile onset. This apparently ignores the two psoriasis onset subtypes as proposed by Christophers and Henseler (1990) and referred to in this review article.

6.3.3 Research with Similar Findings

The findings of this study concur with the research of Henseler and Christophers (1985) that there are two types of psoriasis, based on age of onset, and with a likely separation in the manifestation of the phenotypes at the age of 40 years. Where this study disagrees with their conclusions is in the nature of the familial association of the late onset distribution. They stated that the late onset is sporadic and without familial association, whilst this study shows familial association with the late onset group has the same pattern as the early onset group, but weaker. The suggestion of more than one distribution in onset in psoriasis is not new, Burch and Rowell (1965) demonstrated there were at least two, possibly three, by mathematical modelling, but their results had not been adopted by others.

Some other researchers in Britain, in a study in Oxford (Mallon et al, 1994), found peaks in the onset distribution for psoriasis at 25 -29 years for males and 15 -24 years for females at early onset and a peak for both sexes at 60-64 years. These results are similar to the present study where the modes for age of onset were 21 years and 62 years for males and 15 years and 57 years for females (section 4.3.2). An examination of twins in Australia (Duffy et al, 1993) has shown that where there is concordance for psoriasis, there is also concordance for the age of onset of psoriasis, indicating that psoriasis onset is genetically controlled. Many of the Australian patients are believed to have British ancestry. This finding of concordance for age of onset is in agreement with studies by Farber and Nall (1982) and Brandrup et al (1978).

The evidence for two age of onset distributions in some populations is now being accepted in the British scientific literature (Barker (1991), where Henseler and Christophers' Type I and Type II are quoted.

6.3.4 Final Comments on Bimodality in Psoriasis

This study formally analysed the age of onset of psoriasis which showed a bimodal distribution. For the first time, the numbers of affected relatives associated with each age of onset category in the psoriasis patients was produced (Smith et al, 1993).

These findings of two onset groups in this study governed the approach to the rest of the study in the genetics of psoriasis, in that the data was analysed for the two onset groups as well as for the patients over all ages to compare with other studies.

6.4 **Genetic Models**

Following the findings on familial association in psoriasis (Chapter 4), it was decided to examine the data on the prevalence of psoriasis in different first degree relatives with a view to determining whether there was significant differences between the prevalence of psoriasis in relatives of psoriasis patients and those of controls. When this was confirmed (section 5.2.1) specific genetic models were applied, firstly, over all ages of onset for comparison with other studies, and secondly, in contrast to other studies to date, divided up into early and late onset groups.

The models of autosomal dominance and autosomal recessiveness, both single and double, as well as polygenic and multifactorial models were applied to these groups and compared with other studies.

6.4.1 The Results of Application of Genetic Models to Psoriasis

The prevalence of psoriasis in parents, siblings, and children of psoriasis patients were calculated and compared with these relatives in controls (Chapter 5, Table 1). All the groups were found to be significantly different from controls. In each category, a significantly higher prevalence of psoriasis in the relatives was found in those with early rather than late onset of psoriasis.

The affected number of the psoriasis patients' siblings when 0 parent, 1 parent and 2 parents were affected (only 2 patients in the last category) were compared. When 1 parent had psoriasis 14.8% of siblings in early onset were affected. The equivalent figure for late onset is 8.5% and for over all ages of onset, 13.6%. When 0 parent had psoriasis, the figures were 8.4%, 4.1% and 6.6% respectively (Chapter 5, Table 2 and Table 3). No strong evidence of sex differentials was found.

These basic results were used for application of the genetic models. Neither a single dominant model (section 5.2.2.1) nor a single recessive model (section 5.2.2.2) were found to be consistent with the data.

6.4.1.1 Double recessive model of inheritance

When tested for the presence of two unlinked autosomal recessive genes, using the methods of Steinberg (1952) (section 5.2.2.3) the data for the affected siblings of psoriasis patients was found to be marginally different from the model over all onsets ($p = 0.07$). For late onset the model was a good fit ($p = 0.39$) to the data and for early onset it was significantly different ($p < 0.05$).

A χ^2 test was applied to the expected and observed numbers in the patients, under this model, for when m^2 (2 parents affected), 2mn (1 parent affected) and n^2 (0 parent is affected) were present. Using the frequency of psoriasis in the parents, where this is pr (= m) for 2 alleles, the model was found to be a good fit to the data for late onset patients and a poor fit for early onset, and for over all onsets. However, this is mainly due to the substantial

differences between the expected and observed numbers when 2 parents are affected, and where the observed numbers in the study are low.

The data for late onset is consistent with the presence of two loci under the Hardy Weinberg Equilibrium, but this does not appear to be so for early onset, and over all onsets.

6.4.1.2 Age of onset when 0 parent and when 1 parent is affected

To investigate the differences in the distribution of age of onset when 0 parent was affected and when 1 parent is affected in psoriasis, the data on onsets was analysed by the method of maximum likelihood for the two categories (section 5.2.3). When 0 parent had psoriasis the results showed a bimodal distribution, indicating that both the early and late onsets were present in the patient. The distribution when 1 parent was affected was demonstrated to be a lognormal distribution, that is, a unimodal distribution with early onset predominantly present (Chapter 5, Figures 2(a) and 2(b)). This was compared with the HLA associations found to be present in early onset, reported by Zachariae (1986). When 1 parent was affected in the present study, it was found to have a similar distribution to that demonstrated by Zachariae when an association with HLA-B13, B17 and B37 were present. When 0 parent was affected, the distribution was similar to that demonstrated for when there was a lack of association with the HLA-B locus.

This is consistent with the findings of Henseler and Christophers (1985) that early onset is associated with HLA-Cw6, since the antigens at the B locus have been reported to be in linkage disequilibrium with HLA-Cw6 (Tiilikainen et al (1980).

It was decided to examine Lomholt's (1963) data on onsets in psoriasis, when 0 parent and 1 parent is affected. These onsets were analysed in the same manner as this study (Chapter 5, Figures 3(a) and 3(b)). The results showed that Lomholt' patients were virtually all those of early onset, whether a parent had psoriasis or not. This would possibly indicate the presence of the B locus and an absence of the late onset, as found in this study, thereby

indicating the possibility of a distinctly different population with regards to the inheritance pattern of psoriasis.

6.4.1.3 Multifactorial inheritance

The results of testing, using the concept of heritabilities, for the presence of a multifactorial element in psoriasis, indicated that this model was consistent with the data over all onsets and the data for early onset and late onset groups separately.

A programme was produced (Chapter 5, Appendix) to estimate, by the methods of Falconer (1965), the heritabilities for over all, early and late onsets and also for different first degree relatives (section 5.2.4.3). These results were then used to indicate the variability occurring with increasing age and the genetic correlation between early and late onset was estimated.

Heritability for early onset was estimated to be 79.8% (excluding children), possibly indicating that early onset is predominantly the result of the additive effects of genes, while 20% of the phenotypic variability is due to non-additive genetic effects and the environment. Heritability for late onset was estimated to be 44.4% (excluding children), possibly indicating that the contribution of additive genetic effects are slightly larger than the effects of non-additive factors plus environment. There appears to be an enhancement of the environmental component for females in late onset, possibly due to the menopause.

The genetic correlation (r_G) between early and late onset was estimated to be 0.75 (section 5.2.5.1). Since this is less than 1, this indicates the possibility that not all of the genes are common to both onset groups.

The liability to psoriasis increases with increasing age (section 5.2.5.2) which would indicate that all the change in heritability between early and late onsets cannot be due to environment influences alone. This would suggest that different genes or a different mixture of genes is responsible or that the same set of genes is present with individual genes varying in their time of action (Falconer, 1967).

6.4.2 State of The Art

The results in this study, for heritability estimations, would indicate that early onset is relatively simple with high heritabilities, indicating stronger additive polygenic effects. This is compared with the late onset which shows lower heritabilities and a more complex hereditary pattern and environmental factors playing a sizeable role (Kassab et al, 1994).

The findings of testing for the model of a double recessive mode of inheritance, shows that early onset is not compatible with this model. Allelic action in late onset appears to conform to the double recessive model.

When the age of onset of patients who have 1 parent and 0 parent affected were analysed, a skewed distribution was found when 1 parent was affected. This was compared with the results of others (Nordberg-Iversen and Zachariae, 1984) and would indicated the possibility of early onset psoriasis having, in part, an association with the B locus and possibly a multiplicative mode of action of the alleles.

The two models of double recessive and multifactorial inheritance of psoriasis are virtually indistinguishable in practice, due to the complex nature of a double recessive model in the absence of specified mating patterns.

The findings of other researchers, who have obtained results consistent with autosomal dominant or single autosomal recessive patterns of inheritance in psoriasis, could well be explained by certain mating patterns within the double recessive model; the exact ones depending on which particular alleles are present in a family or a population. For example, where one parent is homozygous for a double recessive pair of alleles, two possible matings out of the three give a 50% chance of the offspring developing the disease. This is may be where the autosomal dominant pattern that has been reported in some psoriatic families, for example, by Abele et al (1963) has originated from. One of the three possible matings gives a 25% chance of the offspring developing the disease, this is the conventionally assumed mating pattern aabb x AaBb. This could be where a single recessive gene model is shown, such as in the Scandinavian study (Swanbeck et al, 1994).

However, these patterns of inheritance can also be explained by a multifactorial model in which major genes can become more dominant in their role and reduce the role of the minor genes involved in the expression of the disease. Interaction with the environment can alter certain genes and make them predominant or quiescent.

It is possible that there is a polygenic genotype present in psoriasis with two phases of activity in the population studied, which are at least partly triggered by age or environmental factors with both extrinsic and intrinsic features. Morris J.A. (1989) gives an immunological response hypothesis in which the age of onset of psoriasis depends on time needed for chance events to activate the immunogenic system. If it were assumed that some genes involved in psoriasis were under the influence of age factors, then this would allow for quiescent minor genes to be activated over age, and contribute to the onset of the condition.

All HLA studies, as outlined in Chapter 5, are strongly indicative of a multifactorial inheritance model. This is supported by the absence of consistent patterns of inheritance within families and the differing risks to siblings. Twin studies also suggest a multifactorial mode of inheritance as the concordance between MZ twins is well below 100%, indicating environmental factors being important in the expression of the disease. Multifactorial models may be said to be making a non-statement, but they do not exclude dominant, single recessive or double recessive genetic models operating. They also allow for epistasis to become an important determinant.

It is clear that there are racial differences in the manifestation of psoriasis, as shown primarily by genetic studies. On the other hand, some researchers seem to be looking for a global unifying inheritance theory. Researchers in Japan (Muto et al (1988) are quoting the results of studies on populations in the U.S.A., whilst those in the U.S.A. (Watson et al, 1972; Elder et al, 1994) are in turn quoting the study by Lomholt (1963) on the Faroe Islanders. This study, particularly, has been referred to and reanalysed by

others who have tried to fit a specific theory of inheritance for psoriasis to their data, but the psoriasis patients in the Faroes are virtually all those of early onset, and thus has a population which has an apparently different gene pool from that examined by others. Bimodality in age of onset in psoriasis is shown in the present study as was that of Burch and Rowell, 1965 (both British); Henseler and Christophers, 1985 (German); Steinberg et al, 1951 (American). (The study by Farber and Nall, 1974 in America may well reveal bimodality in the age of onset data when the raw data is divided up into 5 year increments or less and formally analysed.) Duffy et al (1993), in a study on twins in Australia, found a correlation in age of onset of psoriasis between concordant MZ twin pairs. This is further evidence that the age of onset of psoriasis is genetically controlled, probably by minor genes varying in their time of action. They stated that most of the ancestors came from a British population.

Any claim to having found "the single model of inheritance" in psoriasis, is at best premature and simplistic. The research of Swanbeck et al (1994) does not help in clarifying the situation, since their study contradicts the previous studies on psoriasis in Scandinavia, carried out to date.

Happle (1994), stated that although a polygenic inheritance theory fits most data best, there are not many genes involved. Epigenic modification may be in operation where the environment alters and activates the gene. There may be a clue to the two types of psoriasis in the presence of two apparent phenotypes in children - naevoid psoriasis and psoriasis vulgaris, which Happle suggests may be due to somatic mutation.

6.4.3 Final Comments on the Application of Genetic Models to Psoriasis

It is possible that there are major genes operating with minor genes modified and controlled by the HLA locus in psoriasis, conforming to different inheritance models in different populations or families. In some populations, such as that studied here, there is also a division in the form of two ages of onset, probably under genetic control, which may indicate the presence of

multiple alleles at two loci. All inheritance models appear to be operating in different situations and may be correct for the particular population or family being examined. However, widespread application of this is inappropriate, and only the most vague genetic counselling is possible as yet.

Psoriasis is probably not static, it is at an evolving state in any population and could be considered to be in dynamic genetic modification, especially in response to environment. This means that, even if major predisposing genetic patterns can be identified in families or in individual populations, the hypothesis of polygenic inheritance with further multifactorial components in the expression of the disease is likely to be the closest we can approximate to a description of its true global state. This would allow for the situation where some genes appear to become prominent in their role, within varying gene pools and environmental influences and giving rise to the mimicking of simple modes of inheritance.

6.5 **Suggestions for further research**

The concomitance of psoriasis and AD needs to be further verified by other researchers in a prospective study of the general population. This would be best carried out by using an agreed set of criteria to eliminate, as far as possible, subjective factors in multi-personnel assessment of the patients. It essentially requires investigation of the prevalence of psoriasis and of AD, and also the prevalence of their co-existence. The patients would either need to be selected by a strictly random process or a whole sub-section of the population studied.

It has been suggested that psoriasis may be an autoimmune disease (Fry, 1988; Cooper, 1992). If this were confirmed, this factor may be relevant to the hypothesis in the present study of the concomitance of psoriasis and AD as outlined in section 3.2.3. As previously stated, there has been a report of association between AD , as well as psoriasis, with vitiligo, which is considered to have an autoimmune basis (Fry and Cornell, 1985). The hypothesis diagram

(section 3.2.3) could be applied to other conditions which are known to be inherited and for which co-existence has been demonstrated.

Epidemiological factors collected on the patients in this study provides data for further studies. For example the lifestyles and sociological factors in questions 5,7,8,10 and 52-59 in the proforma (Chapter 2, Appendix A) could be examined fully. This would include different approaches to the relationship of class, smoking , alcohol consumption, diet, caffeine intake, or stress with psoriasis and AD could be carried out, as measured against the controls patients. Research could be related to all these factors in complex multifactorial models of association. Dr J.Y. Kassab, of the Centre for Applied Statistics, has examined some of these factors in relation to psoriasis, and the results are being prepared for publication.

In a preliminary look at the data and assessments of Odds Ratios, the author has found, using univariate analysis, some evidence that social class, smoking, above average alcohol consumption, and a diet which is deficient in white meat, fish, and fresh vegetables are all risk factors for triggering or exacerbating psoriasis. Risk factors for AD have not been assessed, but the diet of AD patients contains less red meat, alcohol and caffeine and these patients smoke less than either psoriasis or control patients. There may be self-imposed factors involved with dietary and lifestyle management in AD patients. More specific levels of all these factors can give risk "cut-offs", for example, is it more than 20 cigarettes a day and more than 2 units of alcohol that is a risk rather than any smoking or alcohol intake being the risk? These levels can be elucidated from questions 52-59 (Chapter 2, Appendix A).

The diagnostic criteria for either psoriasis or AD, given in Chapter 3, Tables 6-10 could be used in complex models which attempt to answer such questions as "What constitutes a psoriasis/AD patient?". Although the features have been given in decreasing order of statistical significance in each of these tables, it may be possible to assign them to groups of criteria

considered to be the most clinically relevant and graded accordingly. A step in this direction has been taken with the comparison of features of one inflammatory condition with another, that is psoriasis and AD (Chapter 3, Table 10), instead of just controls. A statistician may be able to pinpoint the statistically significant features, but it is essentially a task for a dermatologist to say which is clinically significant, in their experience in practice.

Since this part of the thesis was completed, a large study has been recently published on the clinical features of AD (Williams et al (1994), but it is not reviewed here.

The ages of onset of psoriasis and the bimodality with the separation at the age of 40 years as demonstrated in this study, needs to be assessed by other researchers in the U.K. In particular, the onsets need to be grouped into classes which are not too coarse to show the distributions, preferably not greater than 5 year increments. Researchers in other countries may well not find two age of onset distributions, depending on the gene pool of the local population. The raw data of Farber and Nall (1974) could be re-analysed and it is possible that there may be two onset distributions demonstrated, especially since there are similarities between the ages of those with psoriasis in the population in their study compared with the distribution calculated as expected from accumulating and correcting the ages of onset in the present study (section 4.5.4).

Any large study should record not only the patients age of onset but also the relatives age of onset, to consolidate the original report in this study that there is a bimodal distribution for the number of relatives associated with the patients ages of onset. These two age of onset could be compared directly to determine whether the two distributions are the same and whether early onset patients have relatives who are also early onset and likewise for late onset. Some evidence for this has been shown in twin studies (Duffy et al, 1993).

Segregation analysis could be applied to the AD patients and their relatives in the same way as that applied to the psoriasis patients. In any such study a multifactorial model should be applied and the heritabilities estimated in order to determine the extent of genetic versus exogenous factors. There may well be parallels with the study of psoriasis. Both are common diseases, so any gene frequency in the population would have to be high. Autosomal dominant gene theory, autosomal recessive gene theory, polygenic or multifactorial inheritance and genomic imprinting have all been postulated for both. Findings and clues found in the search for an AD gene or genes may well be applicable to psoriasis and vice versa.

Heritabilities have been calculated for AD of between 20% and 30% by Küster et al (1990), who concluded that AD has a multifactorial pathogenesis with polygenic inheritance, but with a large environmental component. The environment has been considered by Marcelli-Barge and Aumont (1989) to be the predominant one, and the researchers were of the opinion that "several genetic systems" are acting together.

This theory of a complex interaction between many genetic factors and environmental factors has been disputed by researchers at Oxford. Cookson et al (1988) reported that they had found vertical transmission of IgE hyporesponsiveness, and thus an autosomal dominant pattern of inheritance with a single gene involved, specifically at chromosome 11, region 13. Others have disputed the findings of the Oxford researchers, for example, Hizawa et al (1992); Amelung et al (1992); Lympany et al (1992); Coleman et al (1993).

An editorial by Morton (1992) stated that although a single gene could appear to be operating in certain families, atopy is "clearly multifactorial". A review article (Barnes 1993) stated that the quest for a single gene was unlikely to be rewarding, but all these findings could be built on and expanded, to eliminate this.

The programme written for use in calculations of the heritabilities in psoriasis could be used for many other diseases where there are prevalences in the relatives of patients and controls. Minor modifications to the programme could also enable it to calculate heritabilities against prevalence in the population to increase its usefulness.

The indication of polygenic inheritance in psoriasis means that the probability of any gene therapy being developed is not a prospect in the near future, unless a major gene or genes can be identified. Even if major genes are located, this may only apply to a small proportion of patients, with a very strong family history of psoriasis. However, finding these genes would help the elucidation of the biological basis of the disease and in turn help in understanding the aetiology of the ones who demonstrate multifactorial causation.

Some Publications Resulting From This Study

(Presented at the end of the thesis)

Beer W.E. Smith A.E. Kassab J.Y.K. Smith P.H.S. Rowland Payne C.M.E. 1991
Psoriasis and atopic dermatitis: concomitance and pathophysiology (poster). In. Proc. 5th Int Cong Psoriasis. San Francisco.

Beer W.E. Smith A.E. Kassab J.Y.K. Smith P.H.S. Rowland Payne C.M.E. 1992
Concomitance of psoriasis and atopic dermatitis. Dermatologica: 184; 265-270

Smith A.E. Kassab J.Y.K. Rowland Payne C.M.E. Beer W.E. 1993
Bimodality in age of onset of psoriasis, in both patients and their relatives Dermatology; 186; 181-186

Smith A.E. Kassab J.Y.K. Rowland Payne C.M.E. Beer W.E. 1993
Psoriasis: bimodality in age of onset, expected ages in the population, associated distribution in the relatives (abstract). Proc. Dermatology 2000. Vienna

Kassab J.Y.K. Smith A.E. Rowland Payne C.M.E. Beer W.E. 1994
Familial risk of psoriasis at early and late onset (abstract). Proc. VI Int Psoriasis Symposium. Chicago

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