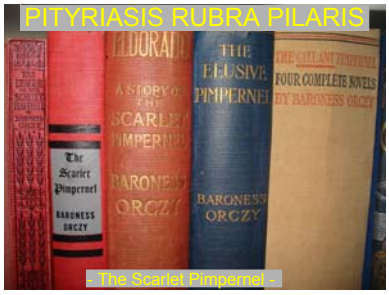
PITYRIASIS RUBRA PILARIS

By

Dr. Andrew Griffiths

This paper is an edited version of the Dowling Oration given in Liverpool in March 2003.

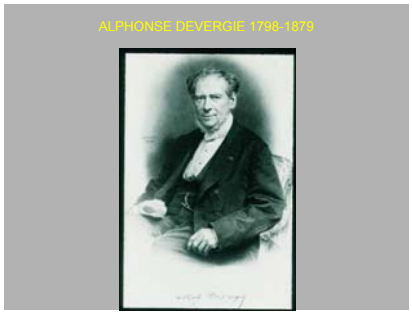
I have chosen the title Pityriasis rubra pilaris –the Scarlet Pimpernel, since like Baroness Orczy's character "they seek him here they seek him there that damned elusive Pimpernel." This disease remains an enigma.



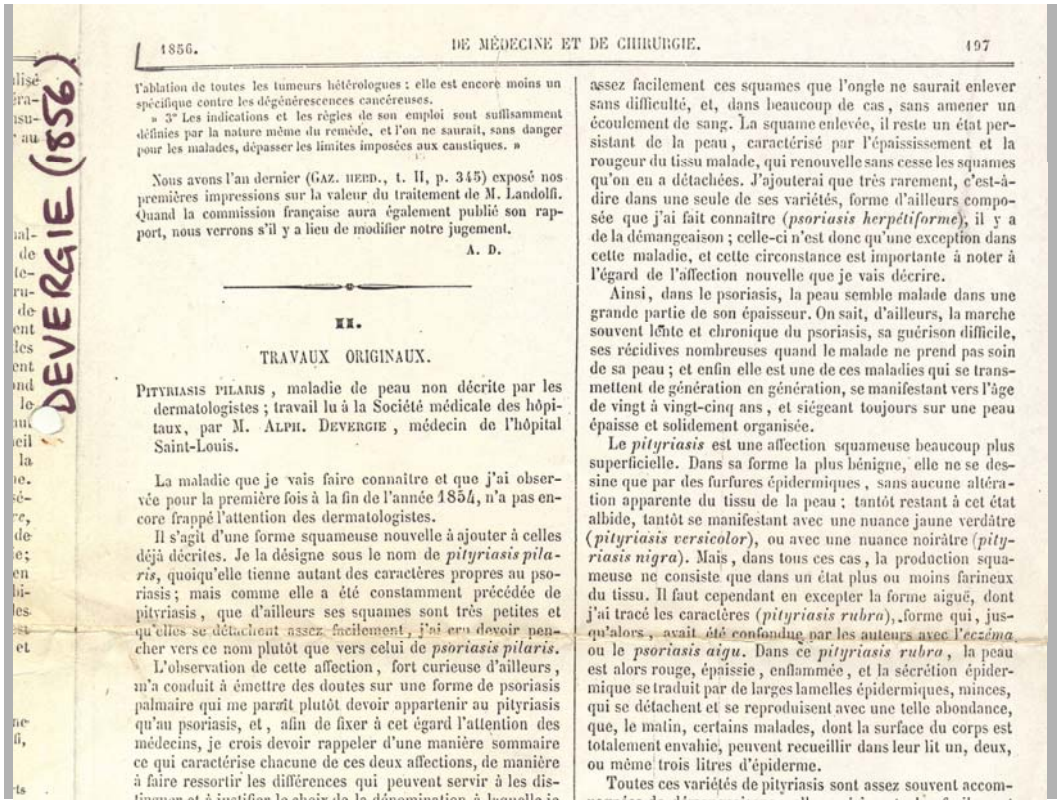
In this paper I will try to summarise my experience of PRP over 35 years. I will try to answer the questions, What **is** PRP? How does the distinctive rash appear? Why does PRP appear?

HISTORY.

The French dermatologist Devergie is credited with the first description of PRP. However I discovered that the first patient was a certain James Shooter admitted to St Bartholomew's Hospital in 1828. He was written up by Claudius Tarral in Rayer's treatise on Skin Diseases in 1835.[1] However the most complete description and that which is taken as the original description **was** given by Marie Guillaume Alphonse Devergie Dermatologist and Forensic doctor at the St Louis Hospital in Paris



in the Gazette Hebdomadaire de Medecine et de Chirurgie in 1856.[2]



1856. DE MÉDECINE ET DE CHIRURGIE. 197

l'ablation de toutes les tumeurs hétérologues : elle est encore moins un spécifique contre les dégénérescences cancéreuses.

» 3° Les indications et les règles de son emploi sont suffisamment définies par la nature même du remède, et l'on ne saurait, sans danger pour les malades, dépasser les limites imposées aux caustiques. »

Nous avons l'an dernier (GAZ. HEBD., t. II, p. 345) exposé nos premières impressions sur la valeur du traitement de M. Landolfi. Quand la commission française aura également publié son rapport, nous verrons s'il y a lieu de modifier notre jugement.

A. D.

II.

TRAVAUX ORIGINAUX.

PITYRIASIS PILARIS, maladie de peau non décrite par les dermatologistes ; travail lu à la Société médicale des hôpitaux, par M. ALPH. DEVERGIE, médecin de l'hôpital Saint-Louis.

La maladie que je vais faire connaître et que j'ai observée pour la première fois à la fin de l'année 1854, n'a pas encore frappé l'attention des dermatologistes.

Il s'agit d'une forme squameuse nouvelle à ajouter à celles déjà décrites. Je la désigne sous le nom de *pityriasis pilaris*, quoiqu'elle tienne autant des caractères propres au psoriasis ; mais comme elle a été constamment précédée de pityriasis, que d'ailleurs ses squames sont très petites et qu'elles se détachent assez facilement, j'ai cru devoir pencher vers ce nom plutôt que vers celui de *psoriasis pilaris*.

L'observation de cette affection, fort curieuse d'ailleurs, m'a conduit à émettre des doutes sur une forme de psoriasis palmaire qui me paraît plutôt devoir appartenir au pityriasis qu'au psoriasis, et, afin de fixer à cet égard l'attention des médecins, je crois devoir rappeler d'une manière sommaire ce qui caractérise chacune de ces deux affections, de manière à faire ressortir les différences qui peuvent servir à les dis-

assez facilement ces squames que l'ongle ne saurait enlever sans difficulté, et, dans beaucoup de cas, sans amener un écoulement de sang. La squame enlevée, il reste un état persistant de la peau, caractérisé par l'épaississement et la rougeur du tissu malade, qui renouvelle sans cesse les squames qu'on en a détachées. J'ajouterai que très rarement, c'est-à-dire dans une seule de ses variétés, forme d'ailleurs composée que j'ai fait connaître (*psoriasis herpétiforme*), il y a de la démangeaison ; celle-ci n'est donc qu'une exception dans cette maladie, et cette circonstance est importante à noter à l'égard de l'affection nouvelle que je vais décrire.

Ainsi, dans le psoriasis, la peau semble malade dans une grande partie de son épaisseur. On sait, d'ailleurs, la marche souvent lente et chronique du psoriasis, sa guérison difficile, ses récidives nombreuses quand le malade ne prend pas soin de sa peau ; et enfin elle est une de ces maladies qui se transmettent de génération en génération, se manifestant vers l'âge de vingt à vingt-cinq ans, et siégeant toujours sur une peau épaisse et solidement organisée.

Le *pityriasis* est une affection squameuse beaucoup plus superficielle. Dans sa forme la plus bénigne, elle ne se dessine que par des furfures épidermiques, sans aucune altération apparente du tissu de la peau ; tantôt restant à cet état albide, tantôt se manifestant avec une nuance jaune verdâtre (*pityriasis versicolor*), ou avec une nuance noirâtre (*pityriasis nigra*). Mais, dans tous ces cas, la production squameuse ne consiste que dans un état plus ou moins farineux du tissu. Il faut cependant en excepter la forme aiguë, dont j'ai tracé les caractères (*pityriasis rubra*), forme qui, jusqu'alors, avait été confondue par les auteurs avec l'*eczéma* ou le *psoriasis aigu*. Dans ce *pityriasis rubra*, la peau est alors rouge, épaissie, enflammée, et la sécrétion épidermique se traduit par de larges lamelles épidermiques, minces, qui se détachent et se reproduisent avec une telle abondance, que, le matin, certains malades, dont la surface du corps est totalement envahie, peuvent recueillir dans leur lit un, deux, ou même trois litres d'épiderme.

Toutes ces variétés de pityriasis sont assez souvent accom-

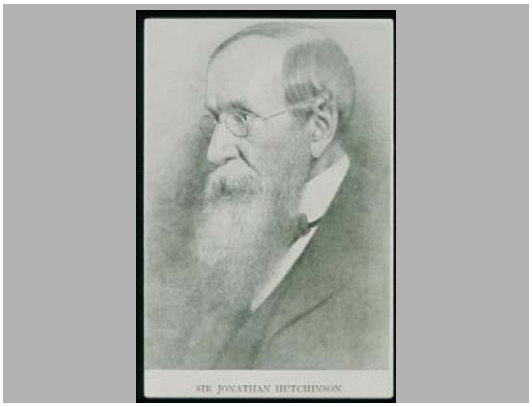
DEVERGIE (1856)

Describing three cases he said “The disease which I hope to make you familiar with and which I observed first in 1854 has not yet caught the attention of dermatologists. It consists of a new form of scaling to add to those already described. I describe it under the name of *Pityriasis pilaris,* although it comprises many of the features of psoriasis; but since it is always preceded by pityriasis and the scales are always tiny and easily detached I felt obliged to favour this name rather than *Psoriasis pilaris.”*

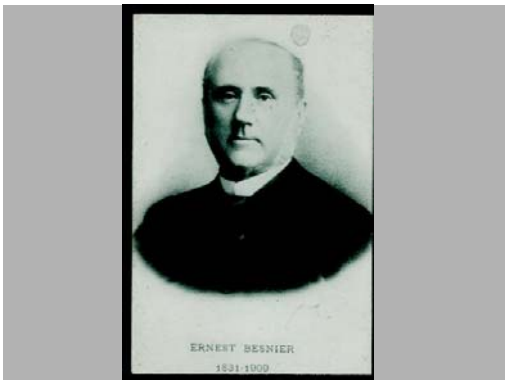
The sequence of the eruption occurred in three phases, Psoriasis palmaris, pityriasis capitis and lastly pityriasis rubra.

•

In 1879 Sir Jonathon Hutchinson reviewed the condition and noted the complete absence of sweating, the tendency to spontaneous remission and the sparing of the mucosal surfaces.[3] The second of his two cases was Eliza Sargeant a patient at the Hospital for Skin Diseases in 1875. In considering the aetiology he did not think that it stemmed from the skin itself but came from either the blood or the nervous system, and citing the marked symmetry, he favoured the latter.

- 

In 1889 Ernest Besnier presented 9 cases and some very clear engravings of the disease.[4]

- 

The article in three parts ran to a massive 120 pages. It did however fix the name of the disease as Pityriasis rubra pilaris. In 1910 de Beurmann from the St Louis Hospital and his two interns described two sisters and two brothers with the disease, although they interpreted the familial occurrence as evidence of its tuberculous origin rather than hereditary.[5]

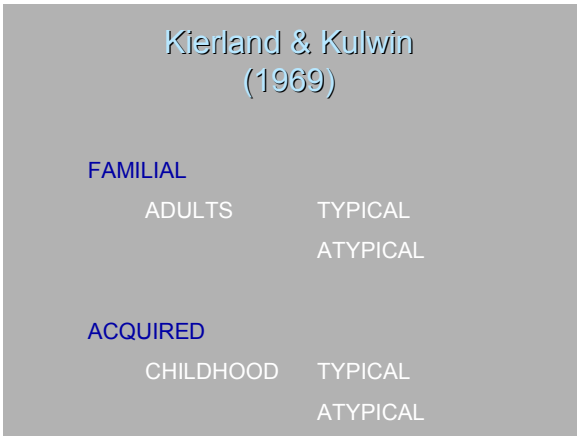
• PRP Older Classifications

Let us now jump forward to the state of things when I started to work on PRP. Kierland & Kulwin from the Mayo clinic classified PRP in 1950[6] as

TYPE I Hereditary - early onset, and

TYPE 2 Acquired -onset in middle age.

57 patients were reviewed by Davidson Winkelmann and Kulwin at the Mayo and the classification was revised in 1969.[7]



- At this point it is a great pleasure and honour to thank Professor Charles Calnan for suggesting that I look at the St John's Hospital material on PRP. I decided to use the existing classification and literature to define an arbitrary score of points for the various clinical features, so that a case with a high score would be a 'Typical' case and vice versa. This avoided my having to accept someone else's diagnosis as accurate, or worse my own diagnosis at that early stage. In addition I collected up as many prospective cases as I could find.

This scoring approach resulted in a distribution seen in Fig. 1 (below). It appears to confirm the suggestion that there is a grouping of cases according to the age at onset.

- It can be seen that the cases shown in red with the highest clinical score have an older age at onset,

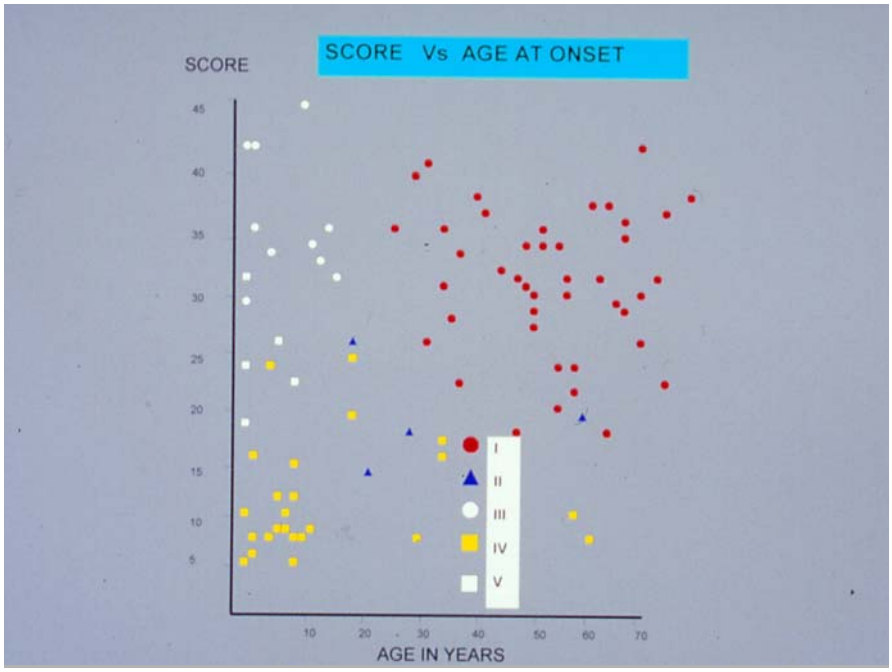


Figure 1

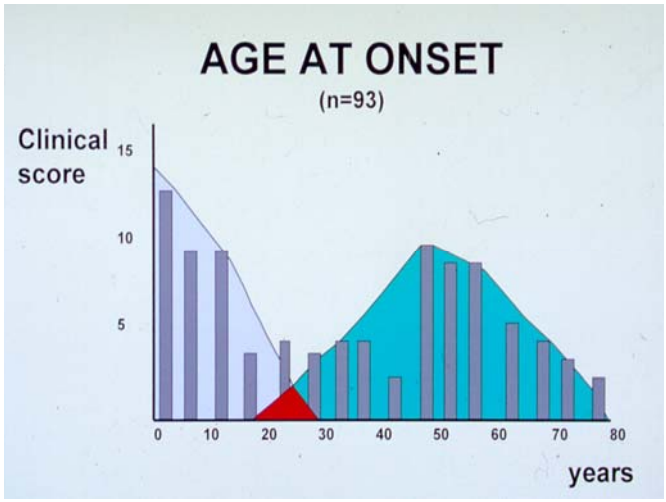
- while a smaller childhood group have equally high scores shown in white dots. These I called Classical Adult PRP and Classical Juvenile PRP respectively.

- There were few adults with low scores associated with atypical features shown by blue triangles

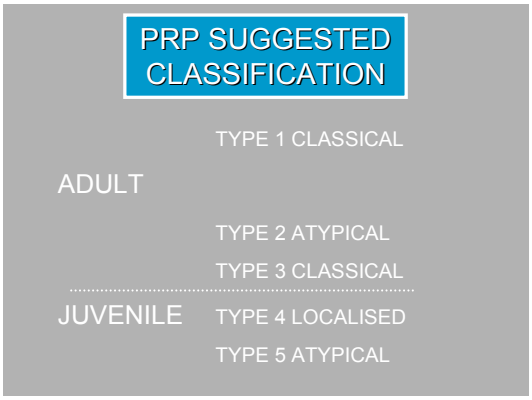
- and very few juveniles with similar scores, the white squares which I classified as Type 2 and Type 5 PRP respectively.

- More numerous however were juveniles with a low score but a number of features with a markedly PRP like appearance of localised follicular plugging on the knees elbows and scattered elsewhere. These are seen as the yellow squares. I called these Type IV PRP or Circumscribed PRP. Since then an AIDS related follicular eruption has been added, but the features do not much resemble PRP.[89]

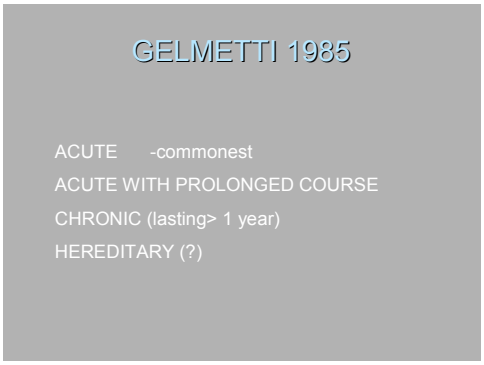
Age distribution. The overall age distribution is bi-modal. You will see that a patient falling in the red area may represent the extreme of either the juvenile or the adult types.



Classification. The classification I proposed was a direct evolution of that of Davidson Winkelman and Kierland.



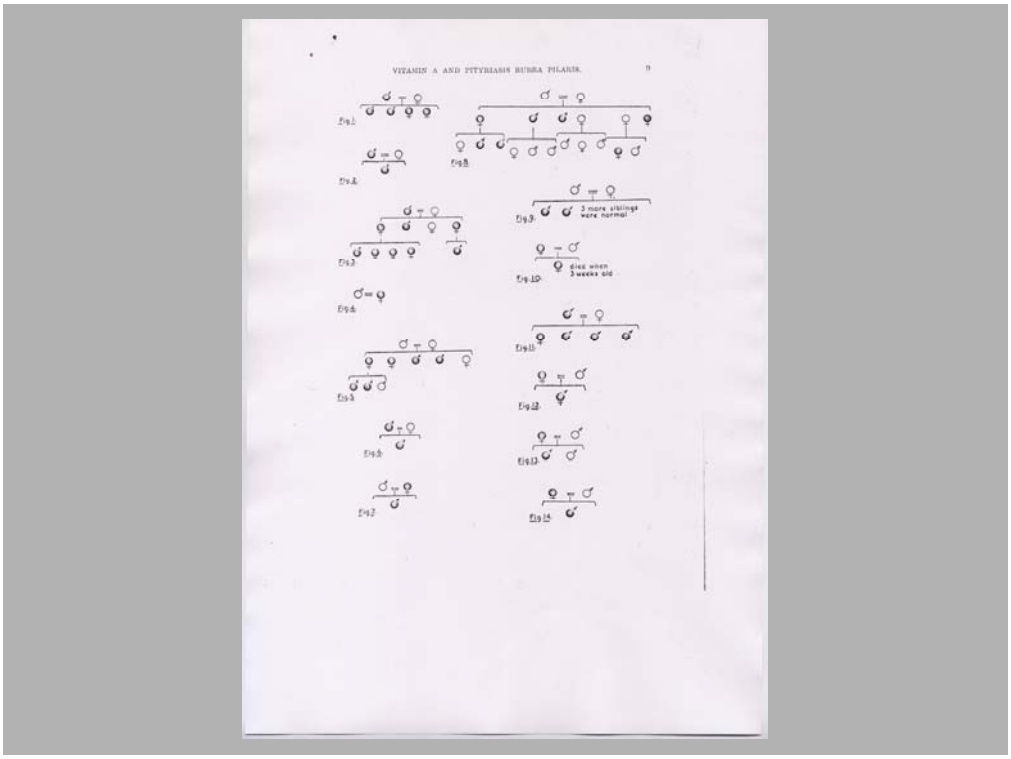
Subsequent experience indicated that there were some shortcomings of this scheme but two other classifications proposed serve less well in practice.[10] [11] For example that suggested by Gelmetti in 1985 from a study of 31 children



would cause difficulties in classifying until observation for over one year to determine the evolution of the disease, and the difference between 'Acute with prolonged course' and 'Chronic' is unclear.

FAMILIAL PRP

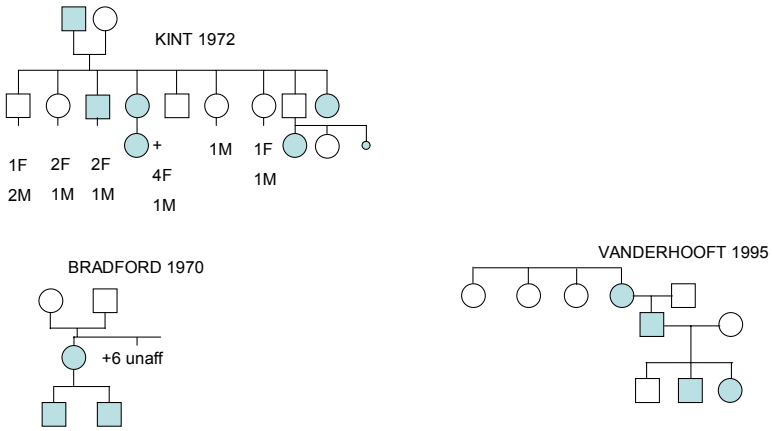
Familial cases of PRP are rare. Leitner summarised cases up to 1947.[12]



Three other reports have appeared since then [131415].

FAMILIAL PRP

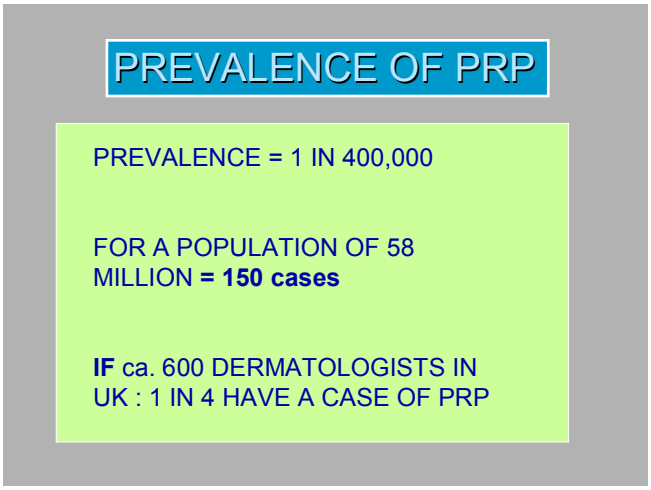
Since 1947



They show an autosomal dominant inheritance.The descriptions of familial PRP in the literature appear convincing but the illustrations which have been published so far are poorly reproduced. I included familial cases in Type V PRP perhaps erroneously with hindsight.

INCIDENCE & PREVALENCE

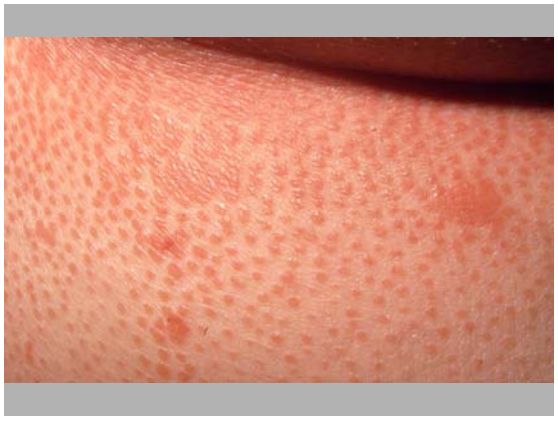
Most dermatologists never have a new case of PRP although they may see one at meetings, so it is clear that PRP is a very rare disorder.



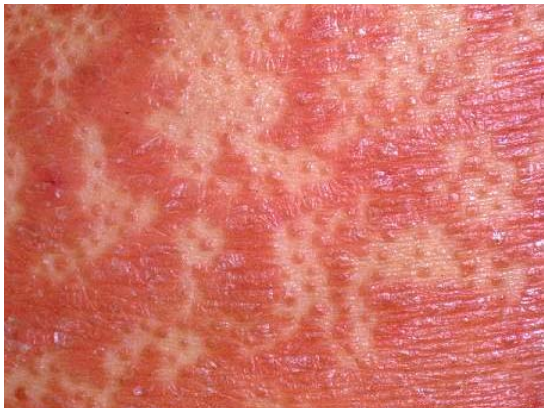
We estimated very roughly a prevalence of 2.5 per million of population, or expressed another way, 1 case per 400,000 of the population. This would mean that there are around 150 cases in the UK at any one time. Assuming there are approximately 600 dermatologists in the UK that means just under 1 in 4 dermatologists may be currently looking after a case. (At this point a show of hands of how many people were currently looking after a case of PRP was approximately 1 in 5.)

CLINICAL PICTURE

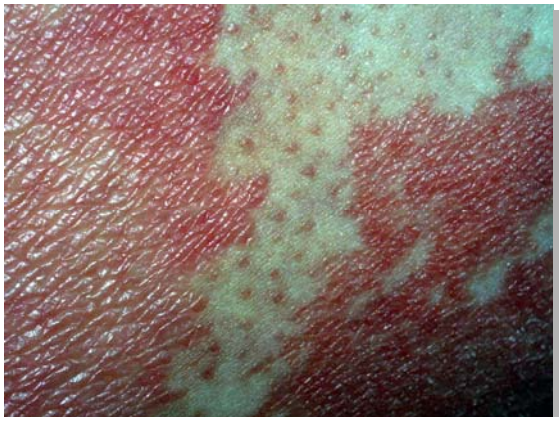
Let us now look at some clinical pictures to give a profile of the types of PRP and how the disease evolves.

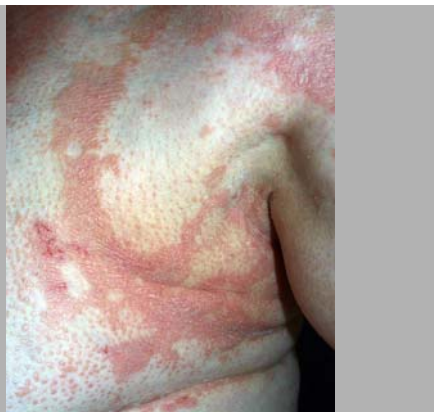


Often an asymptomatic macule of 1 or 2 centimetres appears somewhere on the upper half of the body. A trigger factor is found in only a minority of patients.

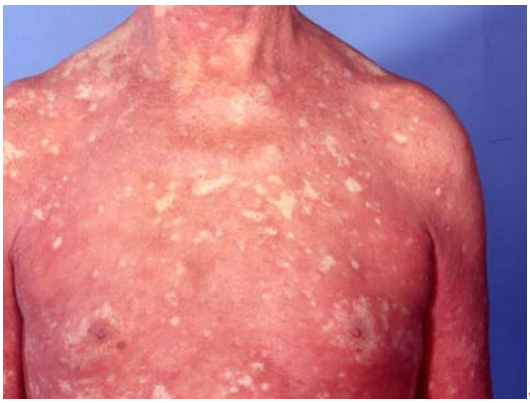


After an interval which can vary from a week to several months further lesions appear.



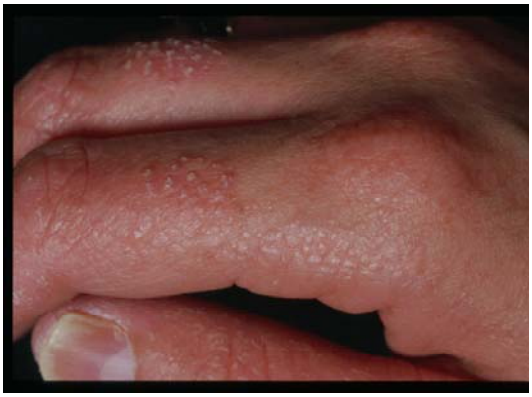


Perifollicular papules and keratinous follicular plugs usually appear first at this stage. Follicular lesions appear first grouped in two's and three's



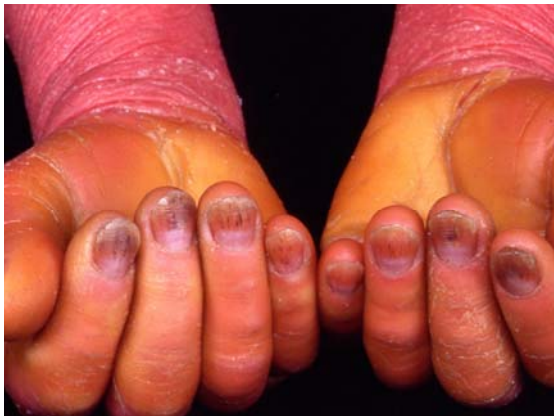
Sheets of erythema

which then rapidly coalesce into sheets of erythema and the process progresses in a cephalocaudal development.



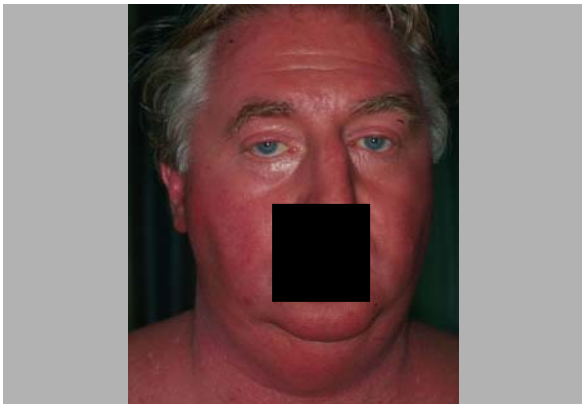
FINGER PAPULES

Follicular papules on the backs of the fingers are suggestive of, but not unique to PRP



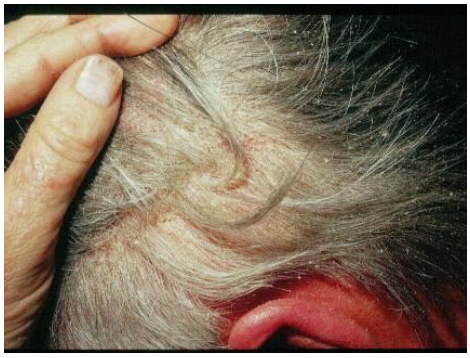
KERATODERMA

In this developing phase the palms and soles thicken forming a yellow keratoderma. Fissuring is a frequent problem.



Ectropion

Confluent erythema affects the face, producing ectropion due to increased epidermal water loss and contracture of the tissues.



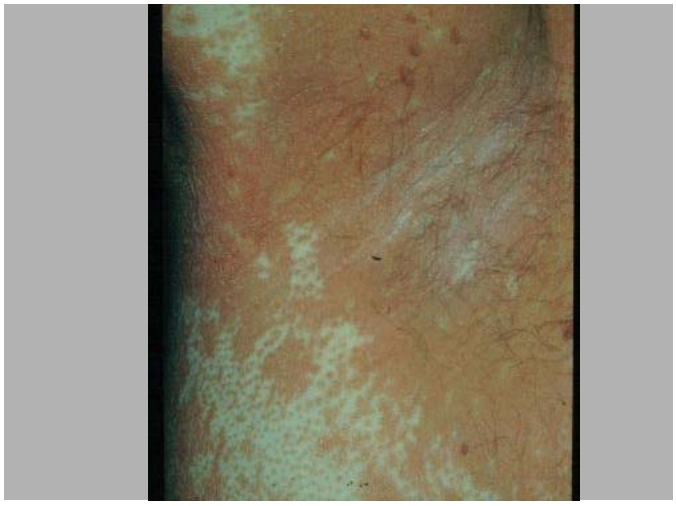
Scalp

The scalp shows profuse bran like scale referred to as pityriasiform, to contrast it with the heavier scale of psoriasis, and the greasy scale of seborrhoeic dermatitis.

Nails

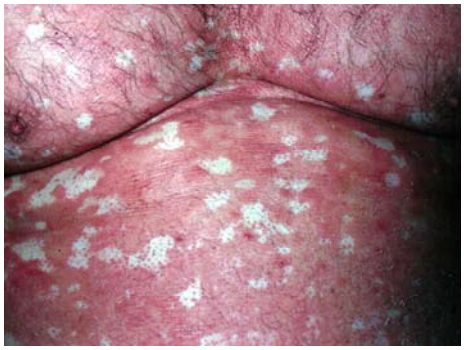
The nails thicken by the accumulation of subungual keratin without any pitting or deformity of the nail plate itself. The typical appearance is the half-and-half nail.

The whole progression from a few follicular lesions to total erythroderma may be fulminating taking only two weeks but is more often two or three months. The erythema has a striking and characteristic orange tinge.



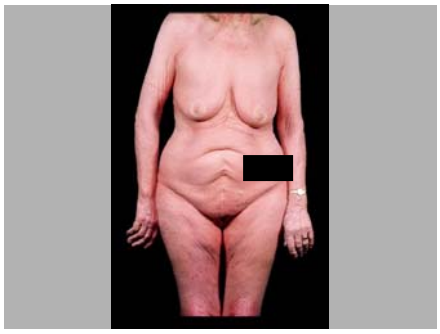
Orange colour

The patient feels marked lassitude. Itching is not a marked feature except perhaps in the early erythrodermic phase. The ability to sweat is often impaired and the vellus body hair shed. Temperature control is lost as expected in any erythroderma.



ISLANDS

Finger-tip sized islands of sparing usually remain.



Periareolar sparing

Sometimes the axillae and the periareolar skin is spared until a late stage in the evolution.

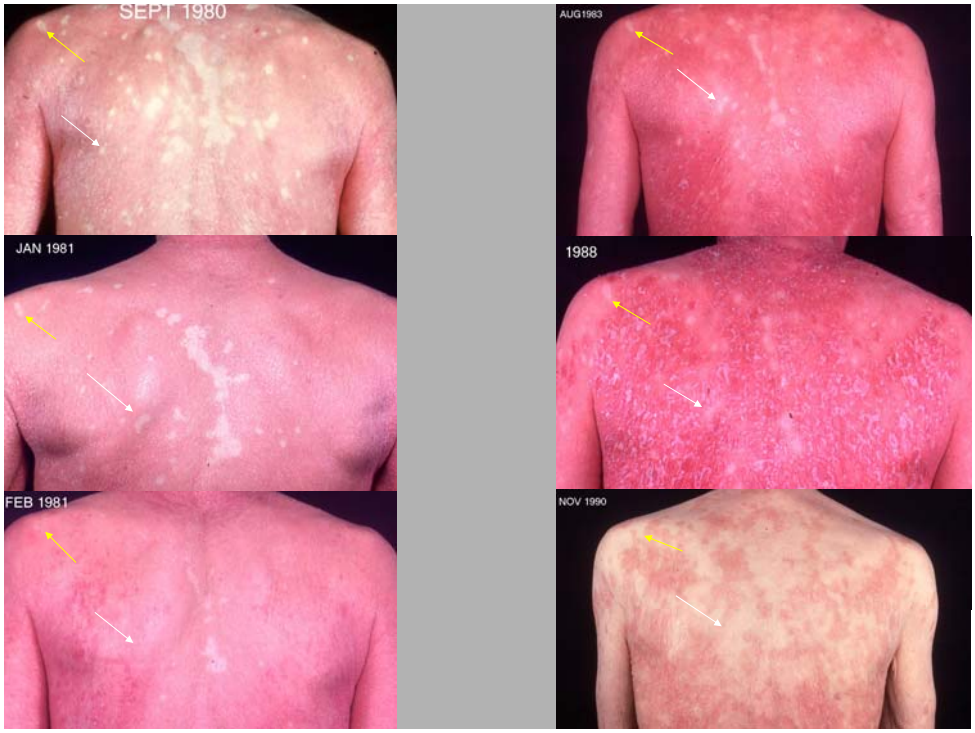


Fig 2 Sequence of Shots showing evolution of the islands

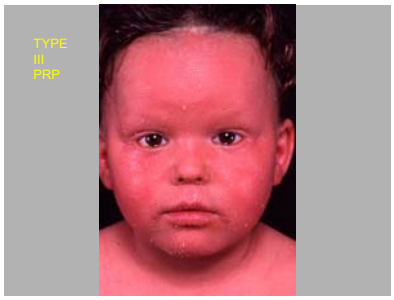
The sequence shown in Fig. 2 illustrates what happens to the islands over a period of 10 years. Some islands disappear whilst others such as those marked by the two arrows are remarkably persistent. Notice also that in the resolving stage in the last frame, the clinical picture is rather similar to seborrhoeic eczema.

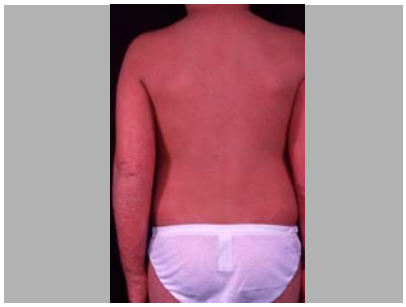
This slide shows the progression to erythroderma over six months. There are often also islands of hyper-erythema appearing as red-upon-red. The disease remains like this in a more or less static state for about two years or longer. Without treatment spontaneous resolution begins slowly with a diminution of the daily amount of scale shed and a lessening of the intensity of the erythema. The patient may feel less tired and notice the return of sweating.

Larger islands of sparing may appear and the whole process begins to fade over 6-12 months.

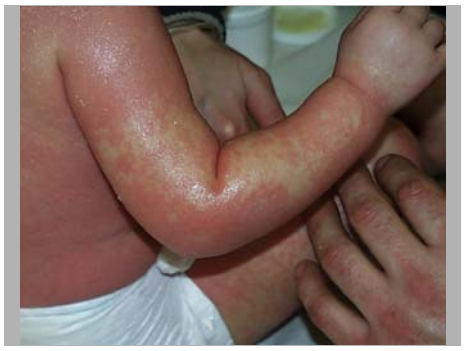
Adults with atypical PRP do not show this remorseless progression to erythroderma, nor does the disease in them show a cephalocaudal spread. Fewer of the signs just described occur but the presence of follicular lesions and the histopathology suggest PRP. I have seen only few of these patients and it is difficult to generalise or indeed to conclude whether they are incomplete forms of PRP.

The classical evolution also occurs in children, that is Type III PRP.

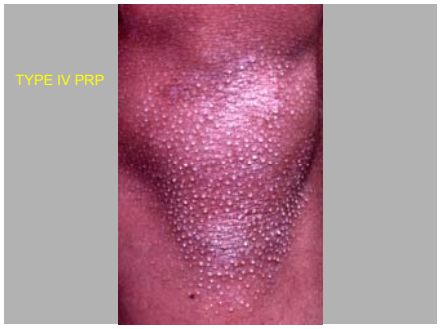




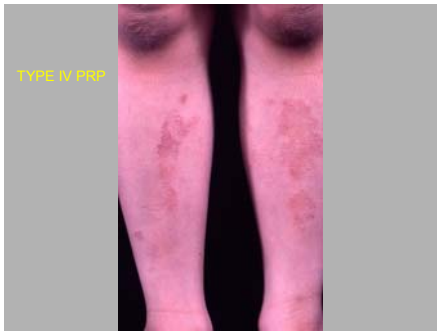
The features are identical to those in adults except for the greatly accelerated rate of evolution. [16]



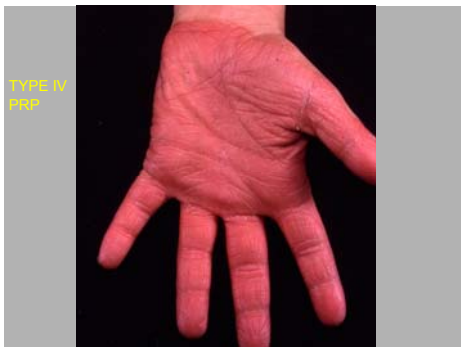
The whole process may be over in 6 to 9 months.



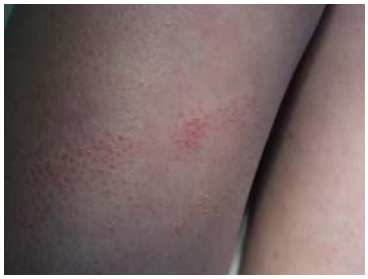
Localised PRP in children or Type IV PRP is clearly different from the above types. It occurs as follicular papules on the knees elbows
and often in patches on the shins.



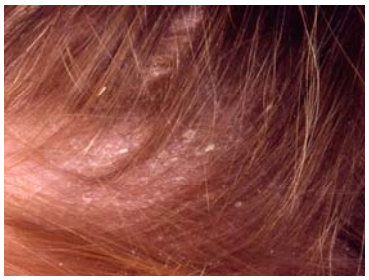
I have seen palmoplantar keratoderma in only a few cases.



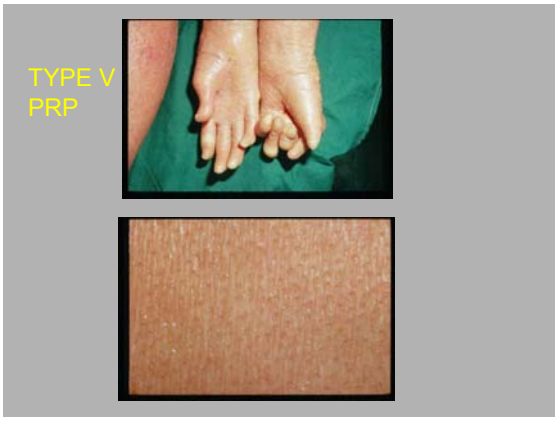
There are often one or two scaly or follicular lesions elsewhere.



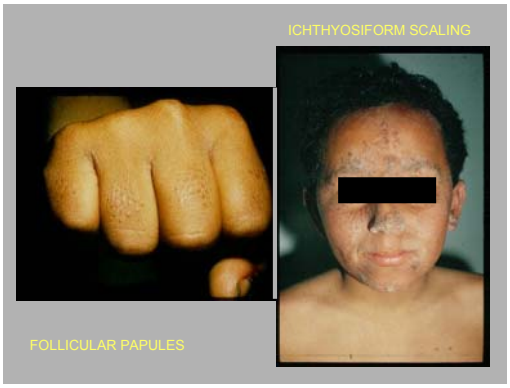
or in the scalp indicating that this is a generalised disease.


scalp

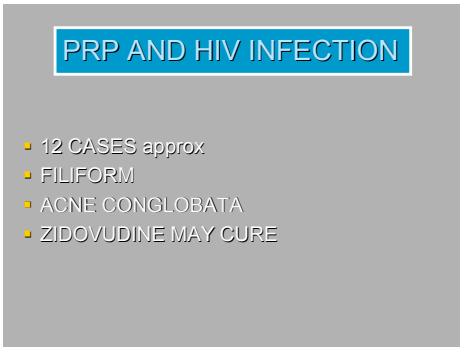
Mild pitting of the nails is seen and the histology is a little more psoriasiform than in the other types. The outcome of this group is discussed below.



Atypical PRP in children need not detain us long. It is excessively rare and almost certainly represents a number of different ichthyotic or erythrokeratoderma-like conditions with prominent follicular lesions but whose features fit better into the diagnosis of PRP than any other dermatoses. A couple of pictures will suffice.



This patient of the late Dr Charles Wells had a generalised follicular eruption but some ichthyotic features also.



A sixth type of PRP associated with HIV infection has been suggested.

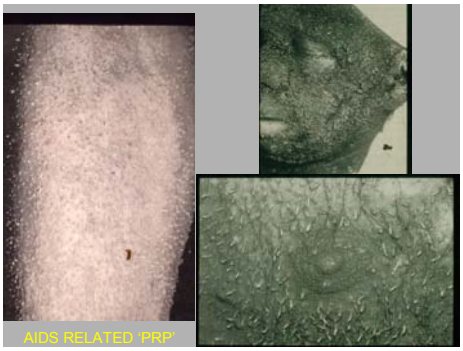


FIG 3. FROM AUFFRET AND BLAUVELDT'S PAPERS

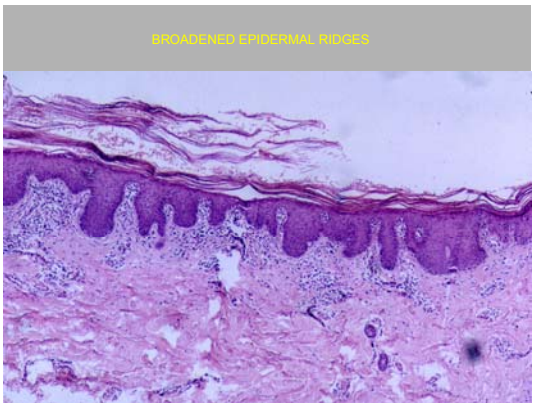
I do not personally believe that this is really PRP. The clinical lesions are filiform keratoses. Fig 3 is a composite of two published cases.

HISTOPATHOLOGY

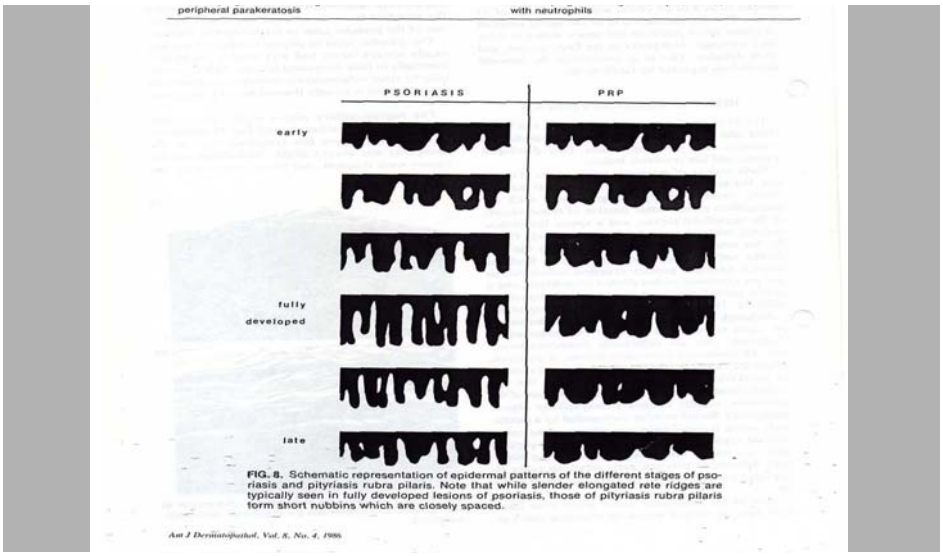
Now is not the time and I am not the person to review the histopathology of PRP. There are several excellent articles on the subject. For those interested in it I recommend these three. [17] [18] [19]

I should not leave the topic however without commenting on a couple of points which are worth mentioning.

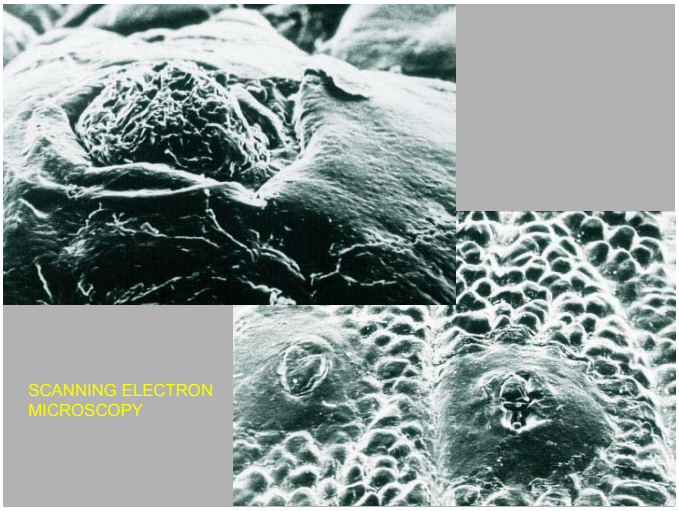
1. The absence of an inflammatory infiltrate and in particular no polymorph microbscesses of Munro.



2. The limited extent of the parakeratosis sometimes called spotty parakeratosis, but which I refer to as ‘stuttering parakeratosis’ to try to give a dynamic time element to what may be the pathological process.

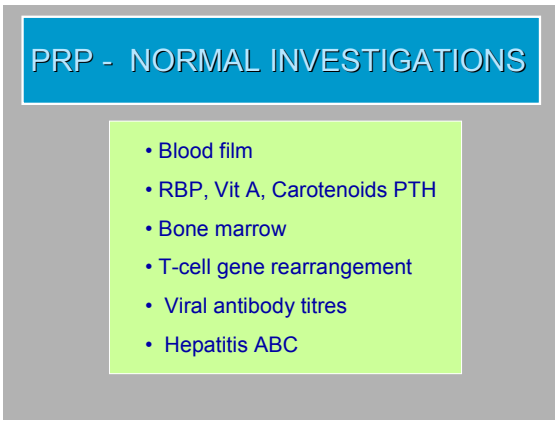


3. The broadening of the rete ridges which is best seen in a biopsy taken from the trunk rather than a follicular papule. The difference in the pattern of acanthosis is shown in the diagram from Soeprono’s paper (above).

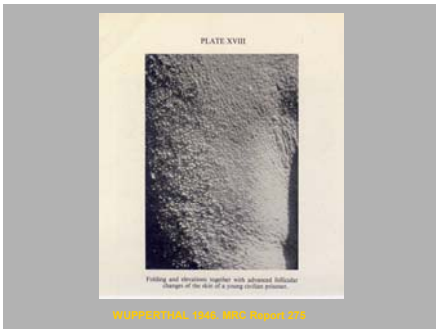


4. No aetiological clues were given by special histopathological techniques, including enzyme histochemistry, scanning and transmission electronmicroscopy, but we obtained some remarkably fine images.

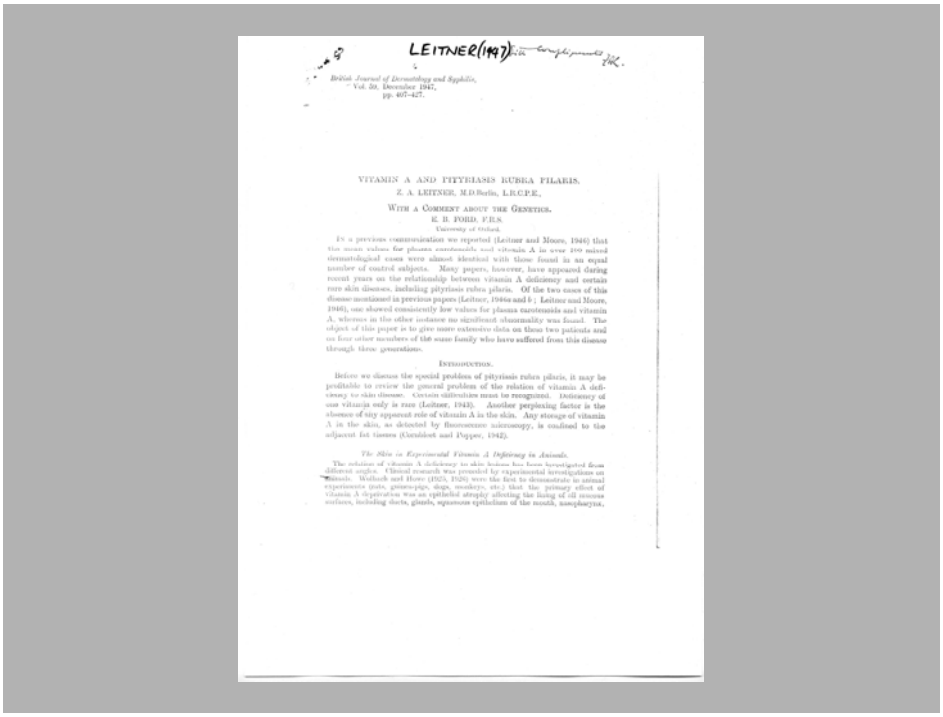
OTHER INVESTIGATIONS



The FBC ESR and CRP are normal. Electrolytes including serum calcium are normal. Two papers suggested an elevation of serum parathyroid hormone but we were unable to confirm this in a series of 12 patients. Autoimmune screening ANA serum proteins are also normal. The ratio B to T lymphocytes in the peripheral blood is normal. A bone marrow in 4 patients was normal. Because the follicular lesions of Vitamin A deficiency so called phrynoderma or goose flesh look rather like the follicular papules of PRP many workers attempted to identify PRP with an abnormality of Vitamin A metabolism.

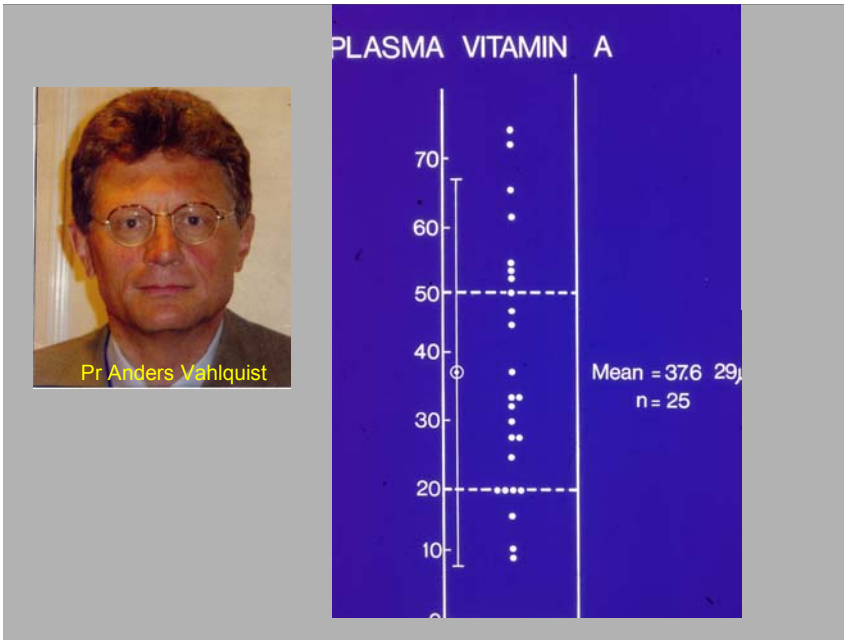


vitamin A deficiency Wuppertal Westphalia



paper on PRP and Vit A

In collaboration with Professor Anders Vahlquist we were unable to find any abnormality of Total carotenoids, Vitamin A or Retinol Binding Protein.[20] [21] Vitamin A supplements do not improve PRP unless given in mega unit doses.



The epidermis in PRP is in a hyperkinetic state.

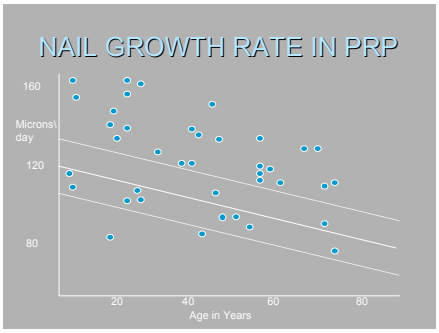
EPIDERMAL TURNOVER AND NAIL GROWTH RATE IS ACCELERATED BY ABOUT 10% IN PRP

This was suggested by the parakeratosis, stratum corneum stripping techniques and by the morphology of villi on the corneocytes seen with Scanning Electron Microscopy.[22] [23]

PRP FLASH LABELLING INDEX (%)

	NORMAL	AFFECTED	ISLAND
	3.0	-	-
Niemi		8.9	-
Marks & Griffiths		27.3	-
Ralfs et al		14.5	-
Griffiths & Pieris		9.65	5.56

Using flash Labelling with radioactive Thymidine we showed that the epidermal turnover rate in affected skin was accelerated by 9%, in affected skin and 5.56% in the islands (for comparison it is 40% in psoriasis).



nail growth rate

This is also reflected in an accelerated nail growth rate,

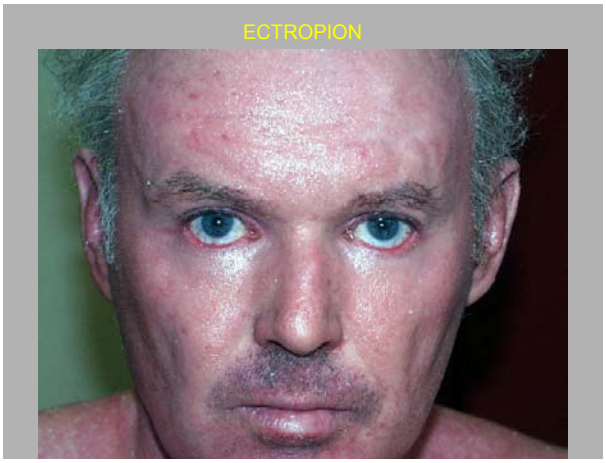

nail end on

which is seen clinically as the thickened half and half nail. The nail plate lies on top of the subungual hyperkeratosis and is never destroyed as it is in severe psoriasis.

COMPLICATIONS

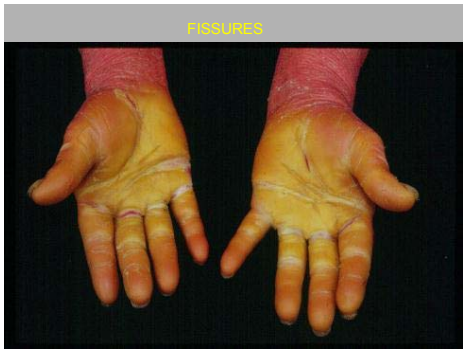
There are very few complications of PRP. Elderly patients may go into high output cardiac failure. This is something to watch out for if you try PUVA treatment. A PRP arthritis is not usually seen. 3 cases have been reported, one of them by Reno Cerio,[24] but it is exceptional. Most problems relate to mechanical and physiological disturbance of the skin.

Ectropion is a common problem best managed by cold saline compresses to the malar region followed by white soft paraffin to reduce the tension on the lower eyelid.



ectropion

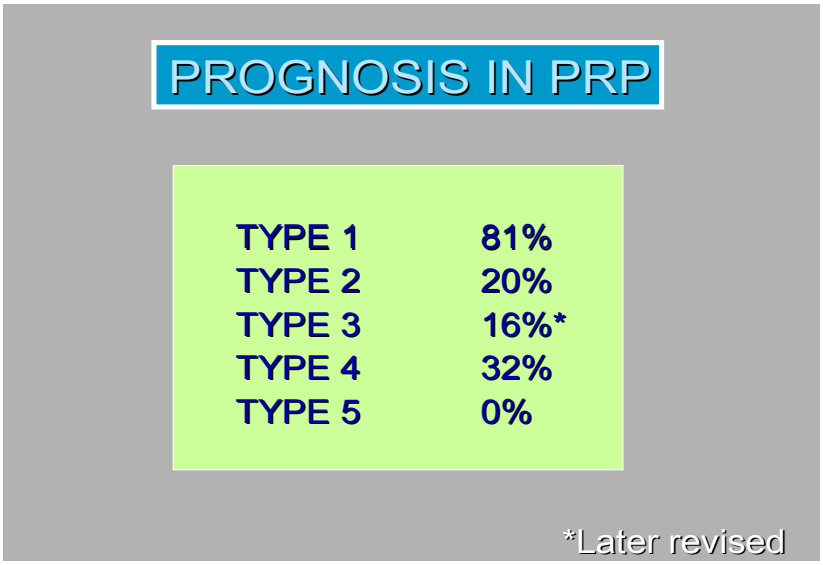
Fissures in the keratoderma are extremely difficult to manage.



Light sensitivity is not uncommon. Inability to sweat and heat intolerance are troublesome in hot weather. Body hair is shed but the scalp hair is usually unaffected.

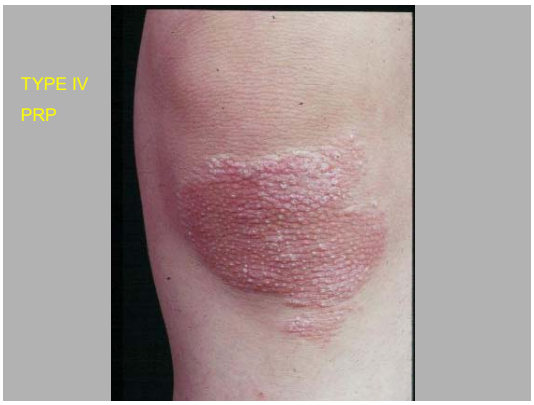
PROGNOSIS

I think that one of the most interesting things to have emerged from our study of PRP over nearly 35 years is a clearer appreciation of the prognosis of the disorder.



80% of patients with Type I PRP clear spontaneously in about three years.[25] Subsequent experience suggested that the figure of 16% for Type III PRP was inaccurate, probably based on the small numbers in the group. It later turned out that it was over 80%, that is the same as the Type I acute cases. In fact the duration of the disease in these children is about 6 months to a year compared to adults of about three years. The children with atypical (Type V) PRP probably have a genodermatosis of life long potential.

Dr Elizabeth Chow and I looked at the outcome of the previously undescribed group of children with localised PRP (Type IV).

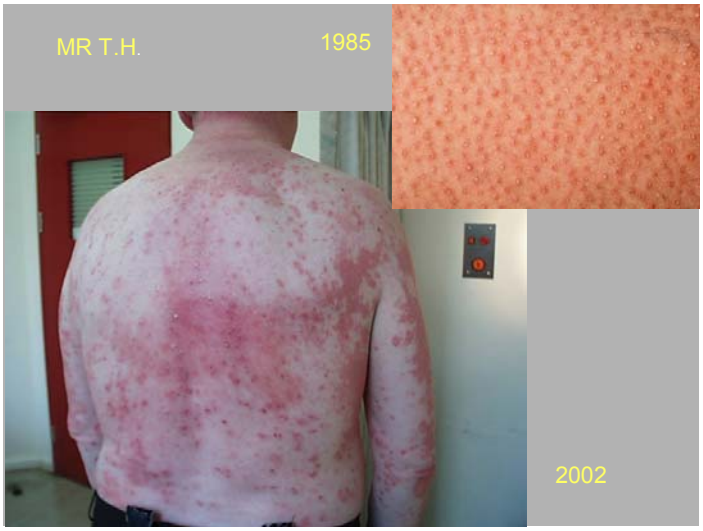


shin in Type IV

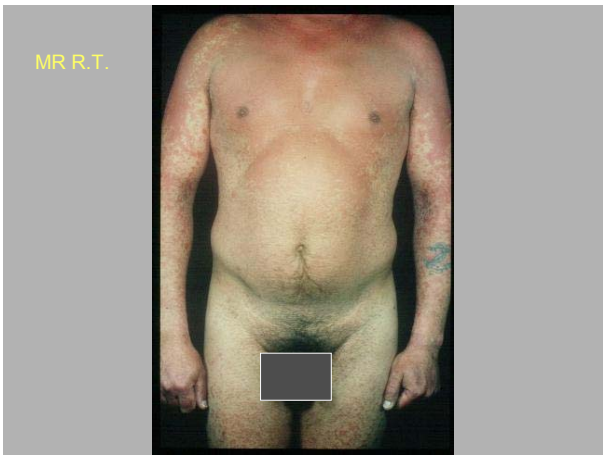
We found that the condition tended to continue more or less unchanged until the late teens when it resolved spontaneously. Most significantly it did not turn into psoriasis despite showing a more psoriasiform histology than other PRP and despite the frequent finding of nail pitting.

If 20% of Type I PRP patients do not clear up, what happens to them?

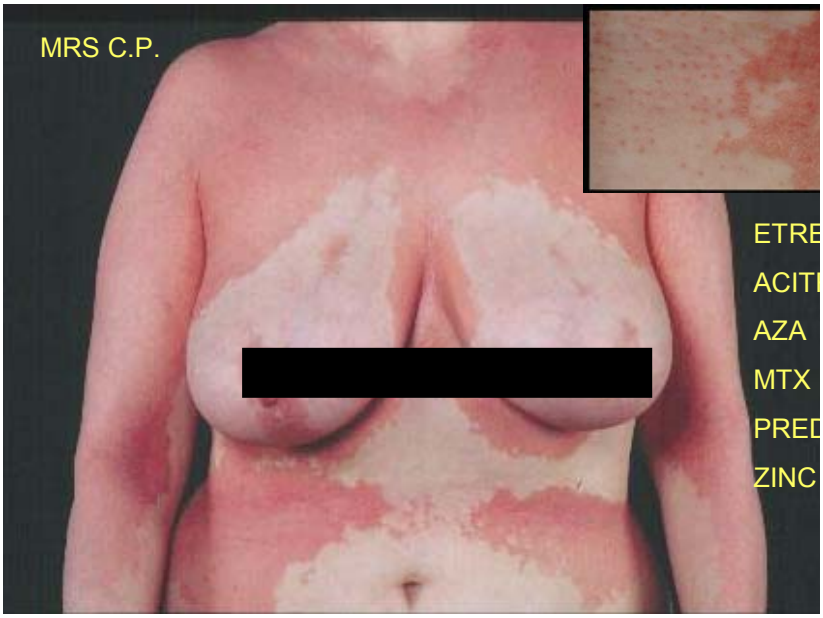
The disease in some patients continues for many years. Some personal observations of individual patients are given to illustrate this section of the presentation based on over thirty years longitudinal study.



I have followed up patient T.H. for 25 years. For personal reasons he did not want to take any systemic medication. After 20 years at the age of 55 his erythroderma began to clear. In the last three years his skin has improved to be less than 10% affected. This possibility may give a small ray of hope to the chronic patient.

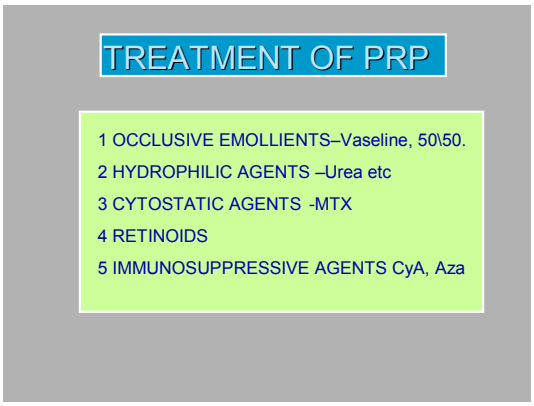


Patient T.H., a policeman whom we showed at the BAD clinical meeting in the 1981[26], suffered from four attacks of absolutely classical PRP at intervals of several years before he was lost to follow up.

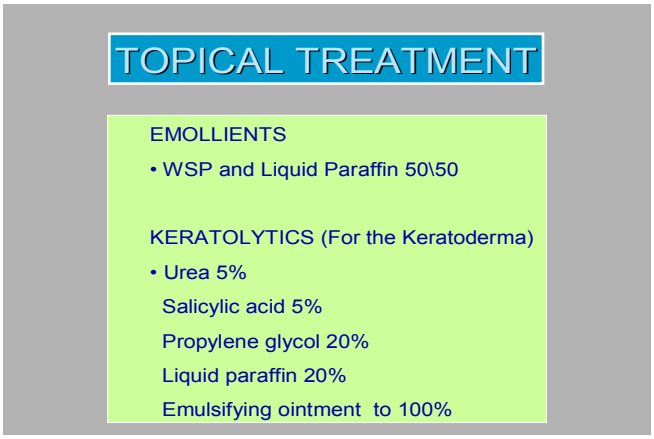


- Patient C.P. had an orange brown scaly patch on the forehead and a smaller one on the chest suspected on morphological and histological grounds of being PRP. They remained static for 6 years and then within a couple of months she became erythrodermic with a cepholocaudal spread. This prolonged interval is rare and the norm is 2-6 weeks. The condition has remained unchanged for 17 years, despite all the systemic treatments listed in the right panel. There are often one or occasionally two initial patches before the appearance of the widespread rash. Does this sound reminiscent of the behaviour of that other Pityriasis, namely Pityriasis rosea? Could we be dealing with a chronic viral infection?

TREATMENT



Most patients require copious topical treatment and many prefer this to systemic treatment.



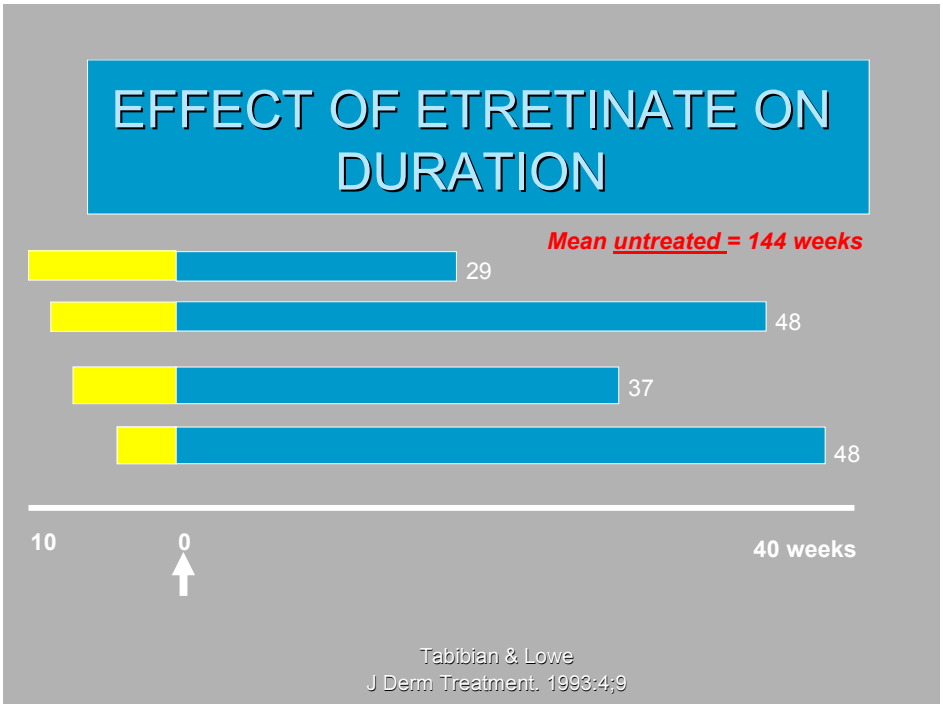
LOCAL TREATMENT

Equal parts of White soft paraffin and liquid paraffin (50\50), and keratolytics for the keratoderma such as the formula listed above may be helpful. A useful strategy is a shower using a liquid emollient followed by a heavy emollient such as Aquaphor . This is a very soothing preparation but it does contain lanolin.

Epaderm™ is a useful commercially available alternative to 50\50.

SYSTEMIC TREATMENT

Unfortunately as PRP becomes established most patients are devastated by the disease and become depressed. Topical treatment gives but little relief and systemic treatment is needed. Systemic steroids rarely work. Of the patients referred to me 9 had been given systemic prednisone and only three showed a partial response, which is of course another difference from psoriasis.



RETINOIDS

About half the patients respond to systemic retinoids whilst the rest which in all respects appear to be indistinguishable from the responders show no response. In those who do respond reducing and stopping the retinoid is not followed by relapse so it appears that Retinoids do shorten the course of the disease.[27] The data here are from Professor Nicholas Lowe for Etretinate.

The drug of first choice is Acitretin. A starting dose of 35 mg increasing in 6 to 8 weeks to 50 mg is sufficient. Above this the increase in mucocutaneous side effects is pronounced.

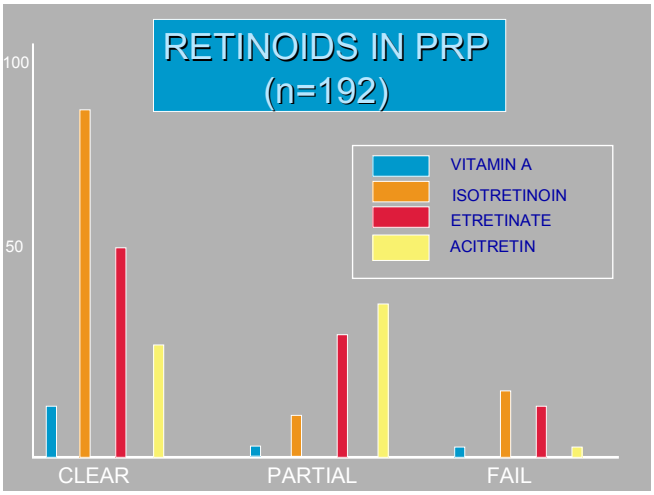
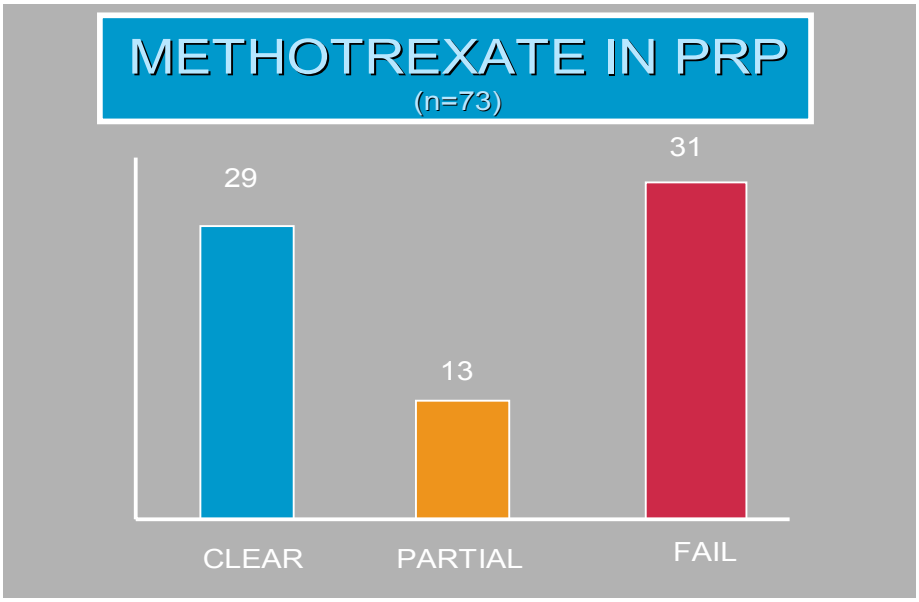


Fig. 4. Table of results of retinoids from the literature

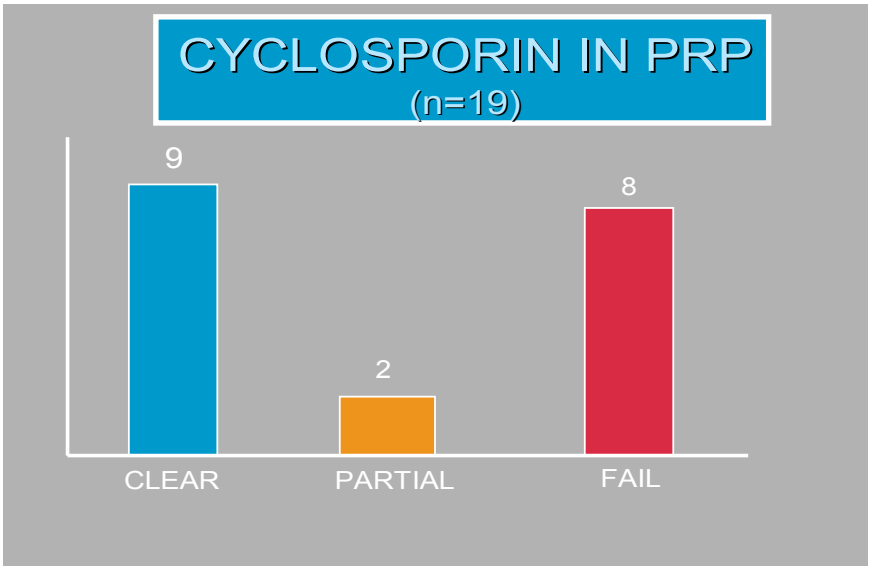
A meta-analysis of the results of retinoids is shown in Fig 4 (above). Whilst allowing for the bias of reporting positive results it does show that there is a significant number of patients who do not respond to retinoids.

Clinically a favourable response is marked by a lessening of the intensity of the erythema, reduction of the daily amount of scale shedding and by the appearance of islands of sparing. An early sign is the reduction of the oedema in the facial skin. Sweating returns and the patient often feels less exhausted. Body hair begins to grow again.



METHOTREXATE

Many different regimes of giving methotrexate have been used in the past making analysis difficult. Many case reports on retinoids mention that previous methotrexate had failed. If we look at the data in the same way we see that methotrexate seems to be effective in something over half the patients,[28] [29] which would be considered a poor result for psoriasis. Is this another feature suggesting that PRP and psoriasis are two different diseases?



CYCLOSPORIN

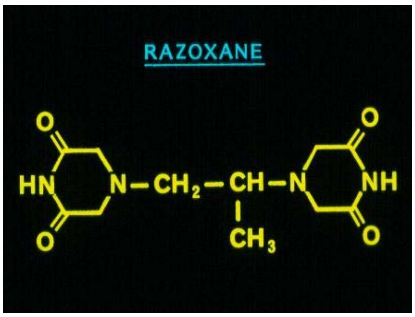
The data on cyclosporin are sparse.[30] Adding eight cases from my own series to those in the literature we have data on 19 patients. Only about half of the patients responded.

PHOTOTHERAPY

Various combinations of ultraviolet and PUVA have been tried mostly with poor results. Few patients can tolerate the increased erythema and itch induced but there are a few reports of success.

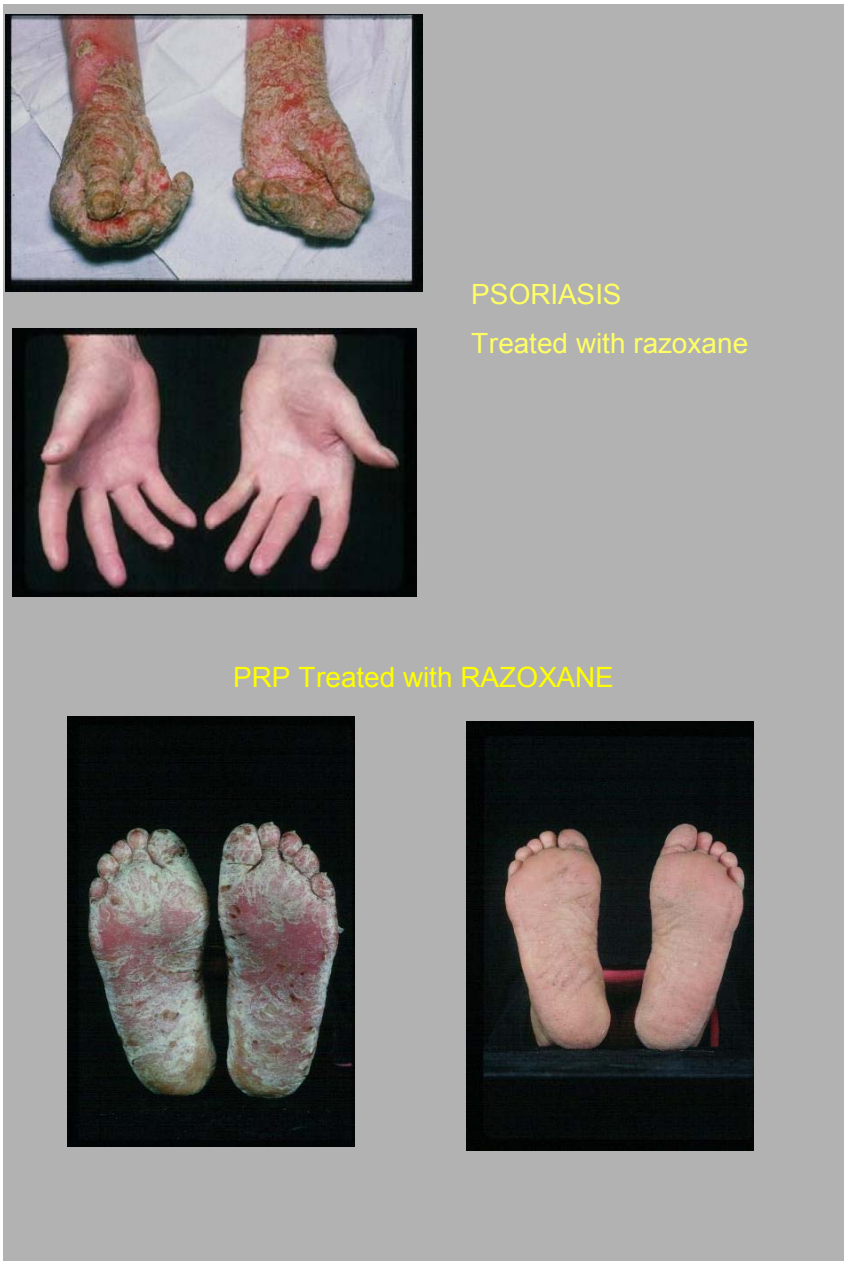
OTHER TREATMENTS

Azathioprine, 6-amino nicotinic acid, stanozolol and a few more appear in sporadic reports. Virginia Hill and I treated three patients with the anti viral drug AZT soon after the time when an AIDS related PRP was reported [31]. The results were negative.



RAZOXANE

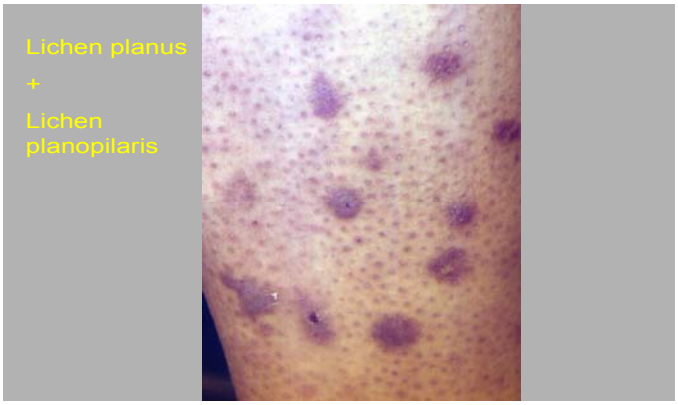
There remain some patients who have incapacitating disease despite all of these therapeutic agents. They are thoroughly miserable and sometimes suicidal.

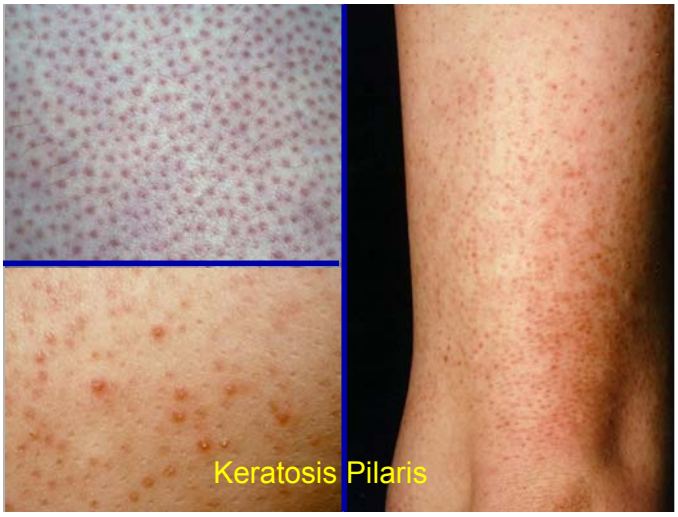


Because of the spectacular results in psoriasis, we treated a group of 12 patients with the anti -cancer drug razoxane and had excellent results with 9 clearing completely within 2 months and with only 2 failures. One showed a partial response. The risk of leukaemia with this drug is well known but almost certainly overestimated.

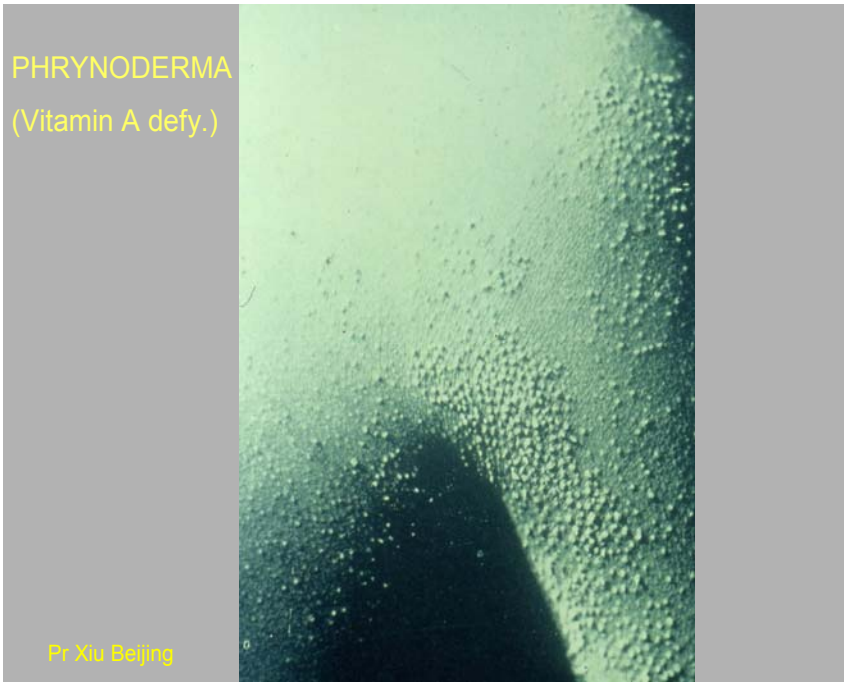
DIFFERENTIAL DIAGNOSIS

There are one or two other conditions which occasionally cause difficulties in diagnosis. Lichen plano-pilaris has the histopathology of LP.

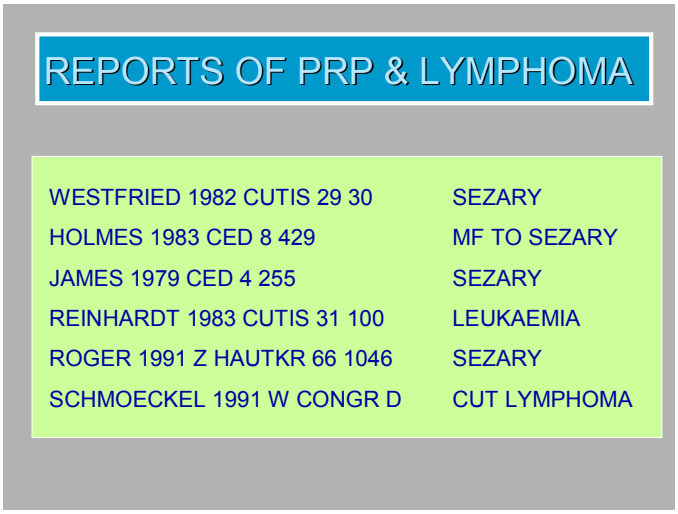




Extensive Keratosis pilaris remains stable and does not show interfollicular erythema. Drug eruptions do not show the orange tinge to the erythema, lack islands of sparing and usually show areas of desquamation especially on the palms and soles.

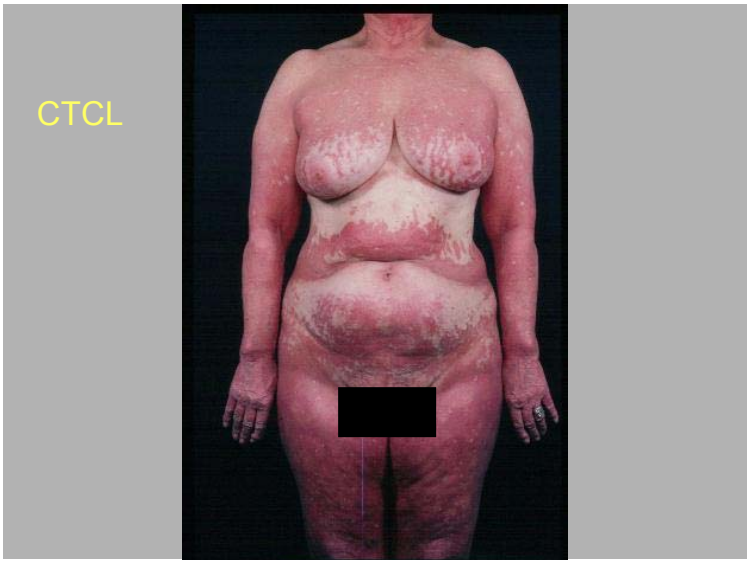


Vitamin A deficiency or Phrynoderma produces rather more exuberant follicular papules than PRP.



PRP AND LYMPHOMAS

Is there a relationship between PRP and pilotropic lymphoma's? This question arises for several reasons. There are reports of PRP turning into a lymphoma, and of a follicular disorder evolving into a Sezary lymphoma.[32] [33] Some of them do look remarkably like PRP clinically. In most of them the initial skin biopsy was non-specific or eczema-like.



- Fig 5 islands in CTCL

Fig 5 shows a patient with known CTCL with PRP-like islands.

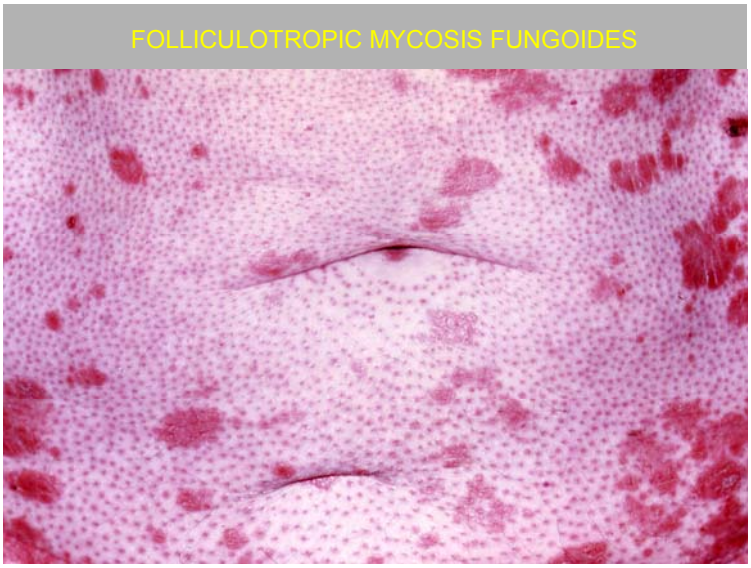
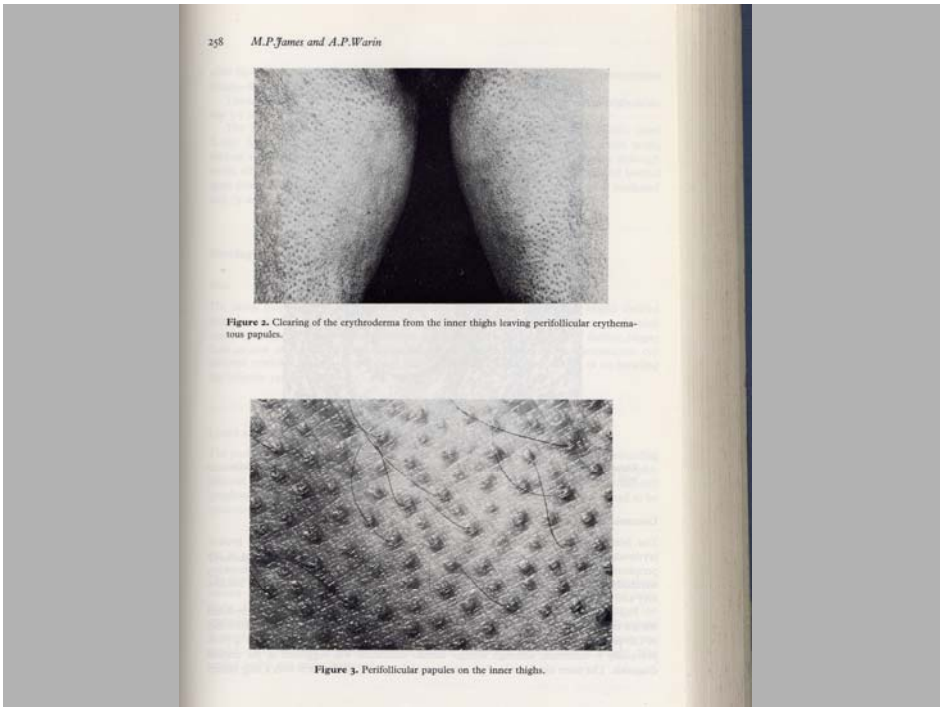


Fig 6 a patient of Prof Martin Black with folliculotropic M.F. which turned into Sezary syndrome.



258 M.P.James and A.P.Warin

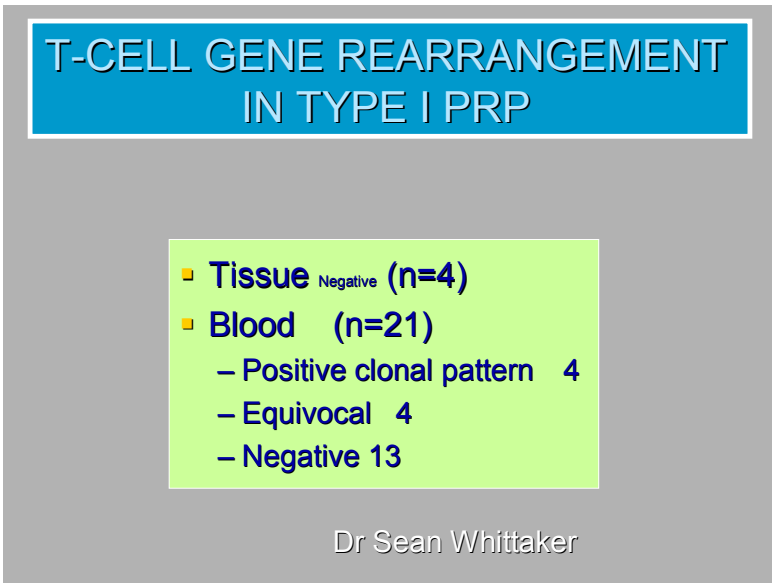
Figure 2. Clearing of the erythroderma from the inner thighs leaving perifollicular erythematous papules.

Figure 3. Perifollicular papules on the inner thighs.

Fig 6.

Dr Martin James published a case of PRP-like Sezary syndrome (Fig 6). Patient B.B. in my series had classical type I PRP which lasted three years then cleared completely. 12 years later he developed CTCL.

Could PRP represent a spectrum of disease resembling that seen in Pityriasis Lichenoides Chronica- PLEVA - Lymphoma?

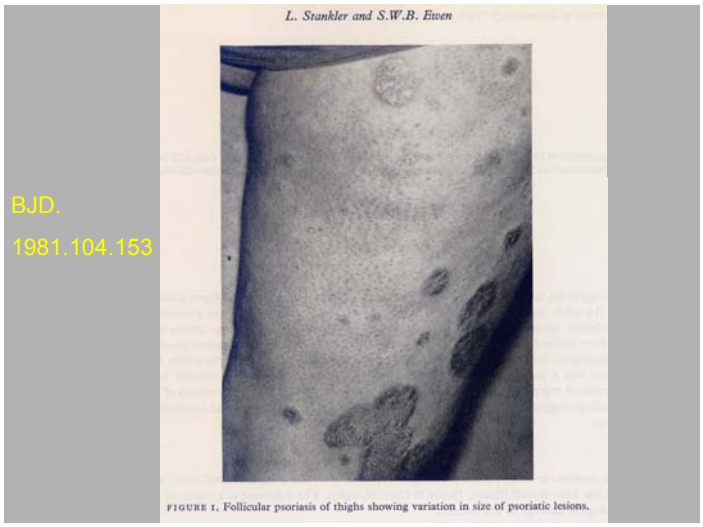


To answer this question we looked at bone marrows in 5 patients. They were morphologically negative. We looked at tissue and blood for T-cell gene rearrangement in 4 patients, and evidence of clonal activity which was negative. T-cell subsets were normal.

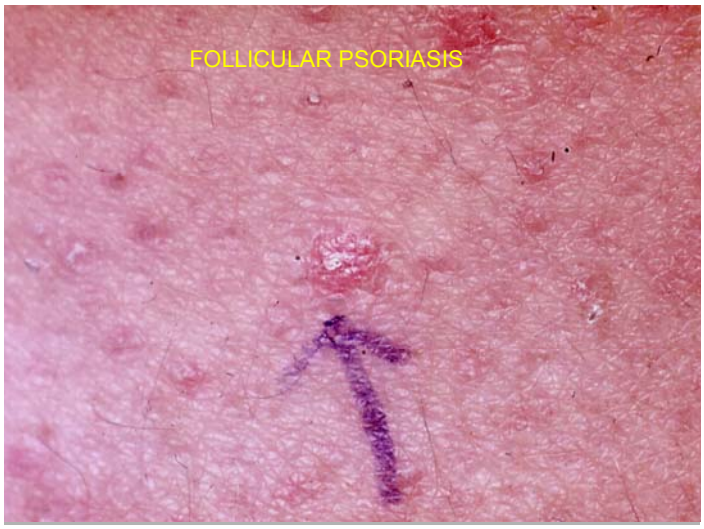
We examined a further 21 blood samples with updated techniques and found only 4 with evidence of a clonal change, 4 with equivocal results and 13 were negative. We must therefore at this stage conclude that it is unlikely that PRP is a form of follicular lymphoma. The similarity in the disease process is however striking.

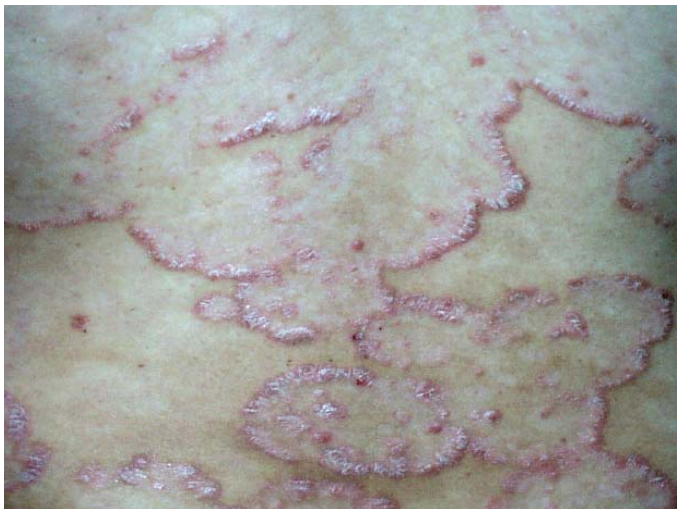
PRP AND PSORIASIS

The relationship of PRP and psoriasis is a difficult problem. Is PRP merely a form of psoriasis? Until we have really reliable methods of defining psoriasis, or alternatively until we know the cause of psoriasis we can only compare and contrast using circumstantial evidence,



Follicular lesions in psoriasis are well recognised but they do not look like the lesions of PRP. Leon Stankler[34] and Stephania Jablonska studied the problem.



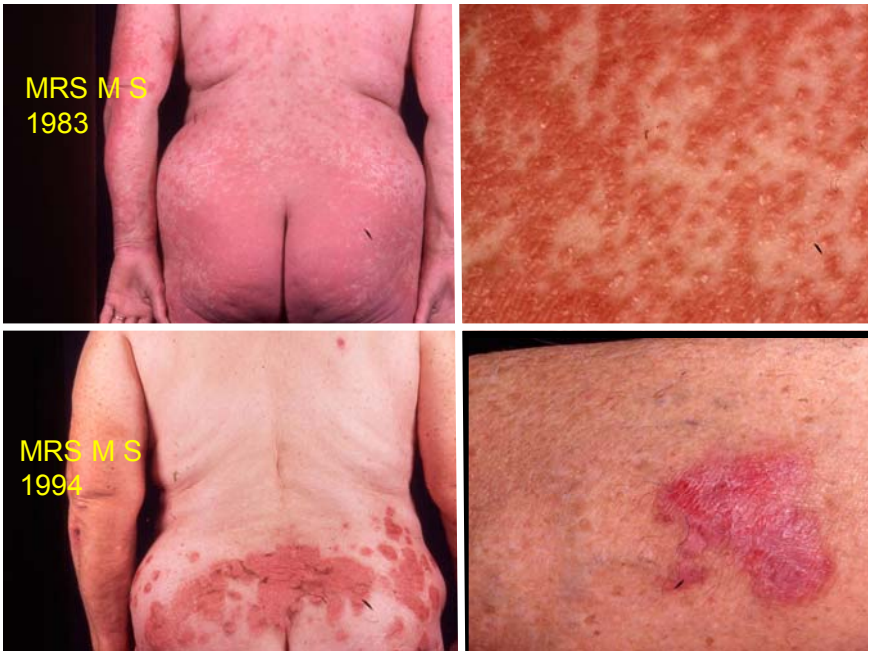


In PRP one never sees the type of lesion with accentuated activity of the disease at the margin. There are many other differences, some of which are listed in theTable.

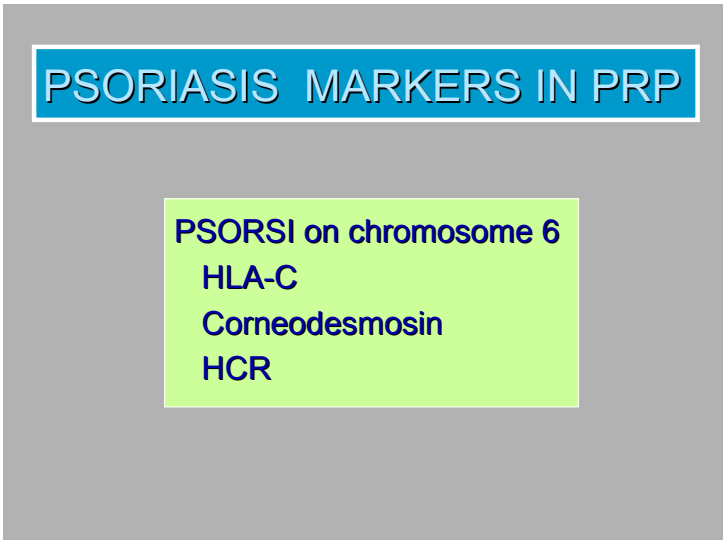
SOME DIFFERENCES BETWEEN PSORIASIS AND PRP

	PRP	PSORIASIS
AGE AT ONSET	BIMODAL	2ND DECADE
SCALP SCALING	FURFURACEOUS	ADHERERENT
KERATODERMA	CONSTANT	LESS COMMON
ISLANDS	CONSTANT	LESS COMMON
NAIL CHANGES	'HALF+ HALF'	OIL DROP
NAIL GROWTH RATE	+	+++
EPIDERMAL KINETICS	+	+++
N'PHIL MICROABSCESSES	-	++
UVB	POOR	GOOD
STEROIDS	POOR	POSITIVE
MTX	VARIABLE	GOOD
ARTHROPATHY	RARE	COMMON

The available evidence points away from PRP being a variant of psoriasis. Nevertheless the problem is clouded by the observation from time to time of cases in which it can be very difficult to decide between the two.



I have seen several patients with classical Type I PRP in whom the acute PRP has cleared over the expected three year period but who retained residual lesions which more and more took over the morphology and histopathology of PRP. The evolution of the rash is shown in one patient (M.S.above) between the top two panels and the lower two over a ten year period.



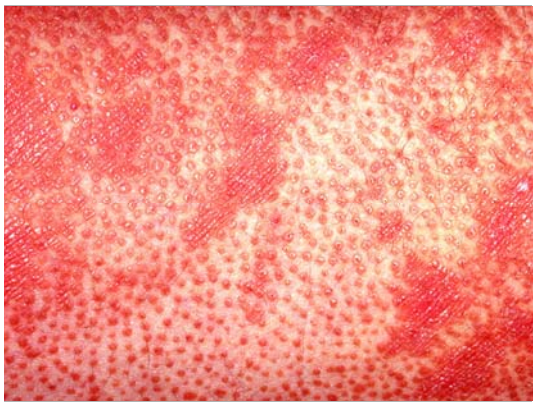
Professor Jonathon Barker and I in an ongoing study are looking at Type I PRP using the most promising DNA markers for psoriasis especially SORSI on Chromosome 6 which includes HLA-C, corneodesmosin and HCR.

AETIOLOGY OF PRP

So now let us turn to the key question of the aetiology of PRP. What have my personal observations led me to think the most likely?

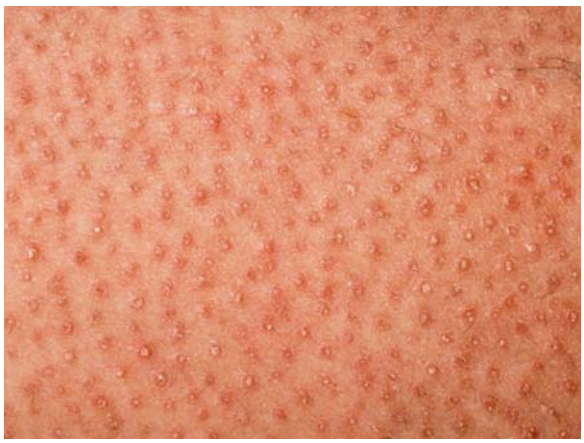
What is the mechanism of production of the rash?

The initial lesion is an erythematous macule soon followed by areas of perifollicular erythema,



PERIFOLLICULAR ERYTHEMA

which only later produce a hyperkeratinised follicular plug. The erythema triggers the localised burst of epidermopoiesis showing first as a follicular plug since the follicle is a column of epithelium. At this stage the **inter-**follicular epithelium shows hyperkeratosis only visible histologically as it does not possess the vertical ‘epidermal escalator’ of the follicle.

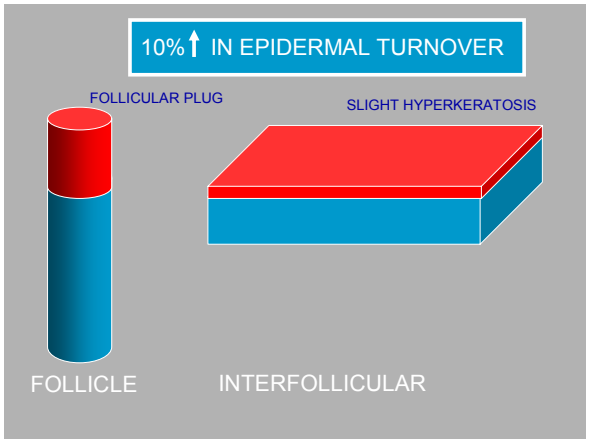


interfollicular erythema

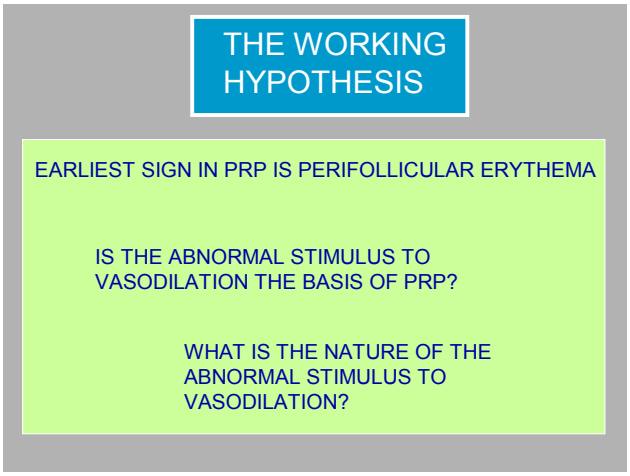
In time the interfollicular epidermis ‘catches up’ with the hyperkeratosis seen at the follicular orifices. This is exactly what is observed clinically as follicular papules coalesce into two’s, three’s then many lesions, producing confluent erythema. This process typically spreads in a cephalocaudal direction since epidermal turnover is some six- to ten-fold more rapid on the head and neck than the legs.

EPIDERMAL TURNOVER AND NAIL GROWTH RATE IS ACCELERATED BY ABOUT 10% IN PRP

An increase of 10% in the stimulus to epidermopoiesis (as found experimentally) if sustained, will in time produce the observed evolution of PRP



First a follicular papule overlying the column of epithelium appears and much less obvious hyperkeratosis over the interfollicular epithelium. Later in the erythrodermic phase the two areas show undifferentiated scaling.

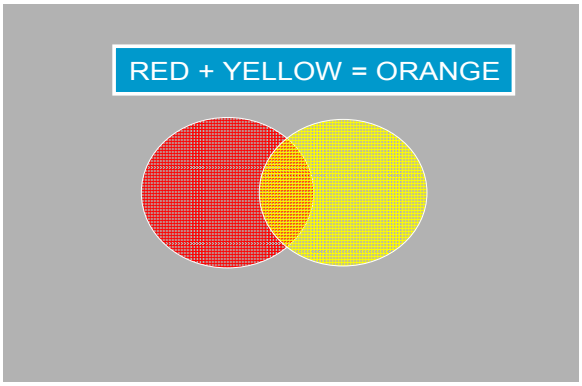


If this supposition is correct the problem can be stated:

- Is the abnormal stimulus to vasodilation the basis of PRP?

- If so, what is the nature of the abnormal stimulus to vasodilation?

We have discounted earlier a mutated T-cell. What else circulating via the blood stream could be a candidate?

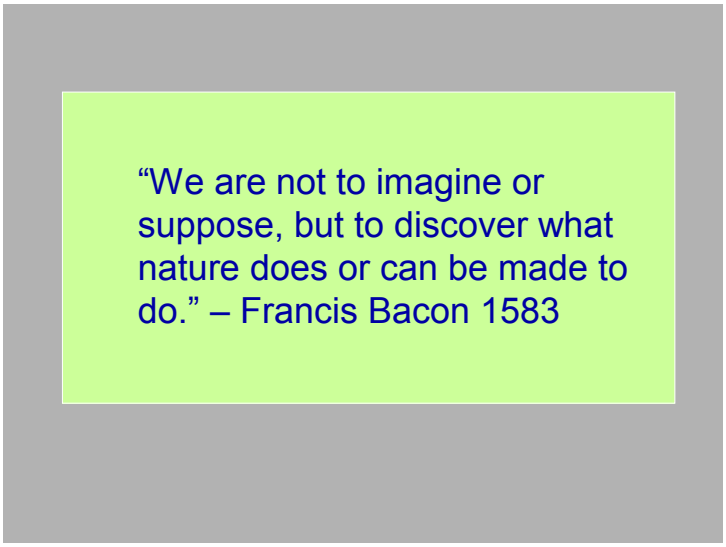


The erythema in PRP shows with a striking orange hue not limited to the palmoplantar keratoderma, so not simply reflecting the thickness of the callus of the keratoderma. Red+yellow=orange. Carotenoids and retinoids are yellow or red but their levels in PRP are normal. Could there be some significance that hypovitaminosis-A induces localised follicular hyperkeratosis with histopathology similar to that of PRP? However we have shown that Total carotenoids Retinol and Retinol binding protein are all normal.

A further feature of PRP is most striking and that is symmetry.

The type of symmetry (see above) does not simply involve the left and right sides but shows an organized patterning and disposition of similar lesions like Rorschach's ink-blot patterns. This points strongly to the involvement of the nervous system as Sir Jonathon Hutchinson observed one hundred years ago.

The absence of a prominent inflammatory infiltrate in the histopathology does not suggest locally liberated mediators but we have not looked for circulating mediators and neuropeptides, a number of which are known to have an influence on cutaneous vasculature and epidermal turnover.
Here I think we shall do well to remember Francis Bacon's words.



CONCLUSION

To conclude we may return to my original questions.

What?

- I think that PRP is now quite clearly delineated.

How?

- By something inducing an accelerated epidermal turnover.

This is associated with vasodilation indeed it is an inevitable consequence of prolonged vasodilation.

Why?

- We are really no nearer to answering this – could a vaso active neuropeptide be responsible? Could PRP be a slow virus infection? A circulating cell with Sezary –like effects?

I hope that I have been able to give you a picture of what PRP is and what it is not. I would have liked to have been able to claim that I have found that "*demmed elusive Pimpernel*" by revealing the cause of PRP, but alas that must await the investigations of better minds than mine.

In conclusion I would like to thank all my collaborators Prof . C.D. Calnan, Prof RS Wells, Prof E. Wilson-Jones, Prof R.M. Marks, Prof RJ Eady, Prof . R. Dawber. Dr Alan Swift, Dr GC Wells, many registrars and referring consultants.
The list here is inevitably incomplete but I wish to record my thanks to all who have encouraged me in working on PRP. Thank you for the honour of allowing me to present this Dowling Oration.

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