Incontinentia Pigmenti (IP) is a genetic disease of the skin, hair, eyes, and teeth. The condition was named for the way that the pigment accumulates in the skin when it is examined under the microscope. IP was reported initially in 1906, but the first complete description was written by Bloch and Sulzerger in 1928. “Bloch-Sulzerger Syndrome” is another name commonly used for IP. Other names are: Bloch-Siemens incontinentia pigmenti, melanoblastosis cutis linearis, and the pigmented dermatosis, Siemens-Bloch type. All these names describe the same condition which we call IP. IP has not been studied in great detail until recently, so the information about it has been both limited and confusing when read historically. This discussion covers what is currently known or suspected about IP but is not conclusive or complete.

Variability

The most prominent features of IP involve the skin and skin derivatives (hair, teeth, and nails). In most individuals with IP, it is a cosmetic problem only. However, some medical reports describe problems with the skeleton, brain and other systems in the body. While these problems may occur, they are probably less frequent than has been suggested in older medical literature. All features or any feature, may vary in severity from person to person even in the same family; affected persons may show different combinations and widely variable severity of features, not only between affected siblings or more distant relatives in the same generation, but also between generations.

The Skin

The most important diagnostic criterion for IP is a progressive rash that has four sequential overlapping stages;

The first stage is the erythematous (red) and vesicular (blister-like) stage, which consists of redness, blisters, and boils. It may be present at birth or may appear in the first few months of life, is the initial manifestation in 90% of patients and may last from a few weeks to a few months. The extremities and the scalp are affected most often, but the rash and blisters can be present on any body part. New crops of blisters may appear at times in the first few months of life and rarely ever later. The rash may be confused with the skin rashes seen in other infectious diseases including chickenpox, herpes, impetigo or scabies. Each of these diseases is more common than IP and can be fatal in infants, so an infant may be treated for an infection before the diagnosis of IP is made. Knowledge of a family history of IP will aid in efficient diagnosis. As serious as it looks, the rash does not seem to be painful, although clothing may irritate the blisters. Secondary infection from common skin bacteria should be treated if it occurs.

The second state is the verrucous (wart-like) stage and the skin lesions look like pustules. There can be either thick crusts or scabs with healing or areas of increased pigmentation (darkened skin). It may be present at birth (implying that the vesicular stage took place in the womb), but it evolves after the first stage in at least 70% of patients. This stage typically lasts months but rarely as long as a year.

The third stage is the hyperpigmented stage in which the skin is darkened in a linear and swirled pattern that has been likened to marble cake. It may be present at birth in 5-10% of patients, but usually begins between 6 and 12 months of life as the verrucous stage heals. The hyperpigmentation may or may not correspond to the areas that were involved in stages I and II. The heavy pigmentation tends to fade with age in most affected individuals; indeed, in some women with mild hyperpigmentation, the swirls may be exceedingly difficult to identify in late childhood.
The fourth stage is the **atrophic** (or cicatricial or scarred) stage. These scars often are present before the hyperpigmentation has faded and are seen in adolescents and adults as pale, hairless patches or streaks. These are most easily seen when they are on the calf or in the scalp because hair doesn't grow in the scarred areas. Once most patients reach adulthood (late teens and beyond) the skin changes may have faded and may not be visible to the casual observer.

**The Teeth**

More than 80% of IP individuals have abnormalities of their teeth and these can be useful in making the diagnosis of IP. Both the baby teeth and the adult teeth may be affected. Frequently, there is a delay in the eruption of the teeth and some teeth may be missing altogether. When they do erupt, the teeth may be small or unusually shaped, typically pegged or cone-shaped. The quality of the teeth and the enamel covering them is usually normal. Few individuals have serious dental problems, but most can be helped with cosmetic dentistry (orthodontics or prosthodontics) when needed.

**The Nails**

The nails of the hands and feet may be involved in up to 40% of patients. That involvement is usually mild and transient. The nails may be ridged, pitted, thickened (called onychogryposis) or completely disrupted. If this feature is present, it involves most or all the finger and toe nails, not just one or two nails. Benign tumors have been described to grow under the nail bed and correspond with the skin lesions seen in stage II. These growths can be painful and may be associated with deformities of the finger bones.

**The Hair**

About half of individuals with IP have minor abnormalities of their hair, usually a loss or thinning of hair (alopecia) on the crown of the head. The alopecia is probably caused by scarring from the vesicular rash, but this is not proven. As with other children, sparseness of hair as a child does not correlate with the quantity of hair as an adult. Hair colour is normal, but the hair may be coarse, wiry, and "lusterless". For the most part, individuals do not have substantial problems with their hair.

**The Eye**

More than 90% of IP patients have normal eyes and normal vision. Some problems, like short and long sightedness, are as common in IP individuals as in the general population without IP. Numerous eye abnormalities in IP have been reported, but the majority of them result from the abnormalities found in the growth of blood vessels in the inside lining of the eye (the retina). The growth of abnormal blood vessels and the associated scarring, bleeding, and detachment of the retina can cause loss of vision, but may be treated if recognized sufficiently early. The mechanisms causing the changes in blood vessels are not fully understood. The natural history of retinal disease in IP is also unknown and optimal treatment of the retinal problems is not clear at present. For this reason it is recommended that all female offspring of affected women and newly diagnosed infants with IP should be evaluated by an Ophthalmologist as soon as possible after birth, monthly until 3-4 months, 3 monthly until one year of age and then bi-annually until 3 years of age. The abnormalities in the retinal blood vessels are highly similar to those seen in premature infants (a disease called Retinopathy of Prematurity, ROP). When found sufficiently early, these abnormalities can usually be treated with one or more approaches; with laser treatment, freezing therapy (called 'cryotherapy') or retinal detachment surgery and/or vitrectomy surgery, depending on the extent and severity of the complication. Rare eye abnormalities have included small eye (microphthalmos), cataract, and total retinal detachment, but these are apparently the consequences of the onset of severe retinal blood vessel disease long before birth. Our knowledge of the natural history of the retinal changes in IP is not complete and the duration of screening remains unclear, therefore ophthalmology review should be continued on an annual basis throughout childhood.

**The Breast:**

Developmental abnormalities of the breast ranging from extra nipples to complete absence of the breast have been reported in IP in a small number of women. It has been suggested that these findings are "at least 10 times greater than the incidence in the general population" but this is not clear.
The Nervous System

One large and retrospective survey of IP done about twenty years ago reported a high frequency of abnormalities of the nervous system (brain and spinal cord) including seizures, paralysis, developmental and mental retardation, and small head size. However, that review seems to have included many persons with conditions other than IP; the real frequency of these problems is probably quite low. A more realistic estimate of the mental or motor retardation is substantially less than 10%. Severe mental retardation occurs in less than 3% of familial cases. An American study of more than 150 affected individuals includes only 2 (1.5%) with severe mental and developmental retardation. While this is not enough information upon which to base strong conclusions, it does imply that the vast majority of individuals with IP will be neurologically normal. Indeed, there is increasing evidence that if problems arise, this happens within the first years of life and only rarely later. Seizures or other complications should be treated as in any other infant, by a Paediatric Neurologist familiar with their management, but they do not need special or unusual therapies. In addition, any child with unexplained seizures, developmental retardation or small head size, should have an imaging study (MRI) to look for abnormal structures or development of the brain.

Diagnosis

If the classic rash is present the diagnosis is straightforward, but it can be more difficult when the rash is mild, when not all the stages are (yet) present or when an adult's skin lesions have faded. A skin biopsy of a fresh vesicular or verrucous skin lesion may show a characteristic pattern of inflammation and degeneration of the skin, but several other skin disorders can look like this, so the biopsy is not a "foolproof" diagnostic test. A skin biopsy of the healed hyperpigmentation that shows the presence of "loose" (i.e. "incontinent") melanin (the brown-black skin pigment) in the dermis of the skin often confirms the diagnosis in the appropriate clinical setting. When there is little or no skin involvement, IP may be assumed to be the diagnosis in individuals "at risk" for the disease if they have other features such as tooth abnormalities, missing patches of hair or overgrowth and scarring of the retinal blood vessels. Such an "at risk" individual could be a woman with two unequivocally affected daughters, the daughter of an unequivocally affected woman or the sister of an affected woman who herself has had the miscarriage of more than one male fetus.

Other Skin Conditions

In recent years, Dermatologists have recognized that NOT all people (male and female) with linear and swirling pigmentation of the skin have IP. The actual diagnosis may be more serious than IP. Therefore, it is necessary to adhere carefully to strict criteria to make the appropriate diagnosis of IP. Accurate diagnosis is important for two reasons: first, as with any medical condition, a person who is given the label or diagnosis of IP, but who actually has something else, may be given incorrect information about management, outlook, recurrence risk and appropriate treatment; second, if persons with more serious conditions are included inadvertently in the surveys and studies of persons assumed to have IP, then any conclusions about the severity and distributions of features of IP will be wrong. For example, if twenty girls with abnormal skin are given the diagnosis of IP and ten of those girls are also mentally retarded, it would appear that mental retardation is a common feature of IP (i.e., half the patients are mentally retarded). On the other hand, if nine of those mentally retarded girls actually have some other medical condition and only one truly has IP, then the frequency of mental retardation in IP is much lower (9% or one out of eleven patients is mentally retarded). As we study IP prospectively and carefully, there is increasing evidence that the latter situation has actually occurred and that IP is a much less severe than has been thought previously.

Some authors suggest that the presence of one or more of the following features may indicate that a person has a condition other than IP: skeletal abnormalities, severe neurologic deficit, asymmetry of the body, severe loss or lack of hair, unusual increased skin pigmentation, extensive decreased skin pigmentation (hypopigmentation) or pitting of the hair follicles (most easily seen on the hands). Based on our experience, we would add the following to this list: abnormal tooth enamel (for example, bad tooth decay or gum disease not explained by poor hygiene), significantly slow body growth and stature, and involvement of internal organs.

Disorders that are somewhat similar to and occasionally confused with IP include focal dermal hypoplasia, infections (caused by herpes, varicella-zoster virus, staphylococcus, or streptococcus), epidermolysis bullosa, linear epidermal nevi, linear and whorled hypermelanosis, congenital ichthyosiform erythroderma,
and congenital bullous mastocytosis. Hypomelanosis of Ito (HI) is also confused with IP, but HI never has bullous or verrucous skin lesions, and the swirled and linear skin is under pigmented compared to the normal surrounding skin.

**The Gene**

All the genetic information that we need is inherited from our parents. The majority of the genes are present as two copies, one of which we have received from each parent. Genetic diseases can be inherited in a number of ways which are referred to as "Mendelian". Recessive diseases show up only when both copies of a pair of genes are abnormal. In dominant conditions, only one member of the pair needs to be abnormal for the disease to occur. A few diseases, of which IP is one, are caused by genes on the X-chromosome and are called "X-linked". This type of Mendelian inheritance is different because all females have two X-chromosomes, while males have only one X (and another, male-determining chromosome called the Y-chromosome). Perhaps the most commonly known X-linked disease is a muscle disorder called Duchenne Muscular Dystrophy. This *recessive X-linked* disease affects only males. (Affected males often are wheelchair confined by their early teens.) Females are not affected since they have two X-chromosomes (one with the disease gene and one with a normal gene); the effect of the normal copy of the gene on one X overrides the effect of the abnormal copy on the other X. Males, however, do not have this second normal copy; they have only one X-chromosome, so they have no way to compensate for their only abnormal X-linked gene and thus they are affected with the disease.

IP is a *dominant X-linked condition*. This means that females with only one copy of the abnormal gene will show the disease, even though they have a normal gene on their other X-chromosome. Males who inherit the abnormal gene (and, of course, do not have a balancing normal copy) do not survive, which implies that the normal copy of the IP gene is extremely important. The function of the normal gene is not known at this time.

A woman who is affected with IP has one normal X-chromosome and one X-chromosome carrying the abnormal gene. At each pregnancy she will give half of her genetic information to each fetus. Thus, for any pregnancy there is a 50-50 chance that she will transmit the X-chromosome with the abnormal IP gene, regardless of the sex of the fetus. On average, half of her daughters will inherit the normal X-chromosome and be unaffected, and half will receive the abnormal X and have IP like their mother. Half of the sons will inherit the normal X-chromosome and be normal, and the other half will receive the abnormal X. Since males cannot survive without a normal copy of the gene, these "affected" males will either miscarry or be stillborn. In summary, half the daughters of an affected IP female will have IP and half will not, but all the live born sons will be normal. This 50-50 chance for affected females is true for each pregnancy, regardless of whether previous pregnancies have been affected or not.

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