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Biochemistry of psoriasis

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The Biochemistry of Psoriasis

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The medical world's first description of psoriasis is that of Celsus, who lived from 25 B.C. to 45 A.D.[1] The disease, psoriasis, is also found in the Old Testament since the word "lepra" includes vitiligo, ichthyosis, elephantiasis, and psoriasis.[2] Psoriasis was first classically described in 1801 by Robert Willan. An accurate description is given in Willan's book The Description and Treatment of Cutaneous Diseases. The following is a quote from his book: "The cuticle is not, however, the only seat of these complaints. They often originate from indurated papulae or larger elevations of the true skin, which by pressure or distention injure the texture of the cuticle, and produce thickened, irregular layers of it. The lepra vulgaris at first exhibits small distinct elevations of the cuticle which are reddish and shining, but never contain fluid. Within 24 hours, however, thin white scales form on their tops. After 3 or 4 days, the small elevations are flattened and at the same time dilated by an extension of their bases to the size of a silver penny. These patches continue to enlarge gradually until they become nearly the size of a crown piece. They always retain a circular or oval form, are covered with dry scales, and surrounded by a red border."[3]

Volumes have been written on psoriasis since the time of Celsus. Gradually, the disease has begun to be understood. As with most diseases, research workers in recent years have been interested with the biochemical nature of this disorder. The following pages will attempt to bring some of these findings together and to put forth what is known concerning the biochemistry of psoriasis. The following subjects will be covered in this paper: minerals, carbohydrates, proteins, esterases, phosphatases, lipids, and dermis.

MINERALS - Microincinerated skin sections are helpful in determining the distribution of inorganic substances. The total ash content of psoriatic lesions is increased above normal, and this may be due to an abundance of calcium salts.[4] There is a high copper content in psoriatic epidermal tissue which may be significant since copper acts as a catalyst in the formation of disulfide bridges during keratinization.[5] Since there is a marked increase in keratinization in psoriasis, the high copper content may explain it.

The potassium content of the psoriatic epidermis is also increased. The potassium concentration is highest when psoriasis is in an untreated, active stage. The acanthosis that is found in psoriasis is probably the process which is responsible for the increased potassium. Studies have not revealed any significant difference between the sodium content of normal and psoriatic epidermis.

CARBOHYDRATES - In 1921 glycogen was identified in the acanthotic epidermis of patients with psoriasis.[4] Glycogen is a source of energy, but its significance in this disease is unknown. It is known that the glycogen is not singularly related to the rate of mitosis, to the acanthotic tendency, or to the high keratinization activity.[6] The accumulation of glycogen must reflect some special aspect of cellular metabolism.

Noncornified psoriatic epidermal cells contain the enzyme phosphorylase. Glycogen synthesis cannot proceed without this enzyme. One may conclude that all noncornified psoriatic cells have the potential of glyconeogenesis.[4]

Originally, investigators wondered if there was a deficiency or an absence of any enzyme in the epidermis of psoriatics. If such an enzyme

deficiency existed, one could postulate a gene directed defect.[7] Studies to date reveal no lack of any enzyme system. Instead, all the enzyme systems were found more active in psoriatic skin than in normal skin with the exception of phosphorylase. This practically rules out a genetic defect in enzyme production. The enzymatic changes of carbohydrate metabolism which lead from normal appearing skin to the lesions of psoriasis are depicted in figure 1.[7]

The width of the arrow signifies enzyme activity. The single black arrow showing the degradation of glycogen to glucose-1-phosphate represents normal activity. Each black line within an arrow signifies a 25% increase in activity.

Psoriatic skin reveals a 40% increase in hexokinase activity. Adenosine diphosphate, a powerful inhibitor of hexokinase, is decreased, while the concentration of adenosine triphosphate, a substrate for hexokinase, is increased.

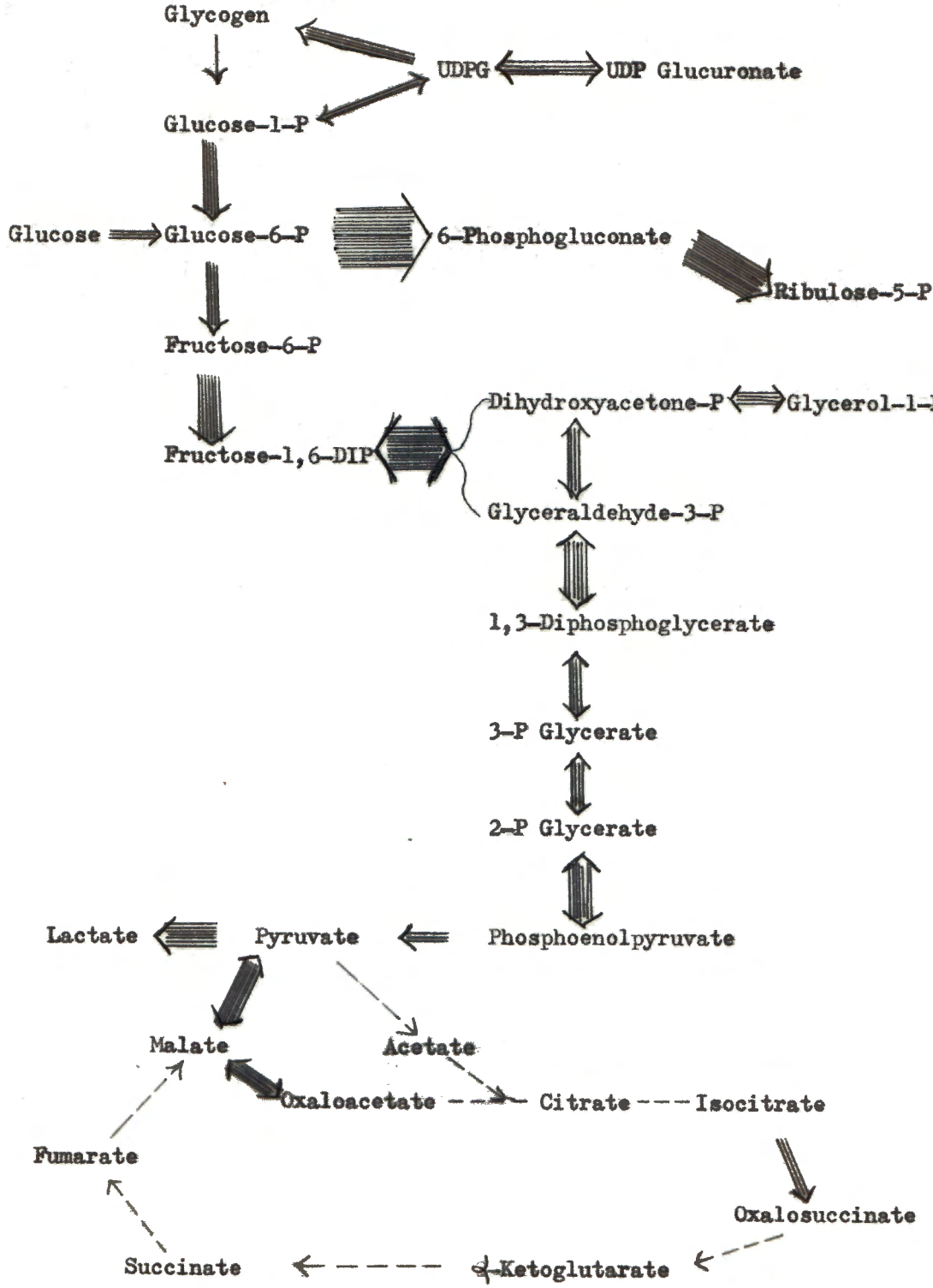
Hexokinase forms glucose-6-phosphate from glucose. Glucose-6-phosphate is metabolized immediately after formation. The normal epidermis converts 80% of glucose-6-phosphate to fructose-6-phosphate and 5% to 6-phosphogluconate.[8] In psoriatic lesions, 15% of the glucose-6-phosphate is converted to 6-phosphogluconate.

Like glucose-6-phosphate, glucose-1-phosphate is rapidly utilized even though its formation is increased by 70%. Glycogen synthetase and uridine diphosphoglucose dehydrogenase were increased by 50%. An increase in the latter enzyme means that the production of mucopolysaccharides is accelerated in the psoriatic scale.[9]

Glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase, enzymes which turn glucose-6-phosphate into 5-carbon sugar phosphates,

Figure 1. Carbohydrate Metabolism in Psoriatic Epidermis

Broken lines indicate unassayed enzymes.



show the largest increases of the enzymes in psoriasis. Nucleic acid synthesis requires the ribose-5-phosphate of this hexose monophosphate shunt. Nucleic acids and their breakdown products are increased in psoriatic epidermis as would be expected from the concentration of these two enzymes.[7] Nucleic acid synthesis cannot utilize all the nucleic acid precursors and pentoses which are produced by this shunt pathway. This is a definite place in psoriatic metabolism where a control mechanism is faulty.

Phosphohexose isomerase converts glucose-6-phosphate to fructose-6-phosphate. With its concentration being increased 45% in psoriasis, the activity of phosphohexose isomerase becomes ten times greater than any other enzyme which competes for glucose-6-phosphate. Consequently, the majority of glucose-6-phosphate is converted to fructose-6-phosphate. Fructose-6-phosphate, in turn, is transformed to fructose-1,6-diphosphate by phosphofructokinase. There is a 125% increase in phosphofructokinase activity in psoriatic scales over normal epidermis.[7]

The changes in carbohydrate metabolism observed in psoriatic lesions apparently reflect a reorganization of the psoriatic cell to allow cellular multiplication. This reorganization is so vast that practically every enzyme system in carbohydrate metabolism is involved.

PROTEINS - The skin owes its protective features to the topmost levels of the epidermis. Protein is the primary component of this protective layer.[10] After synthesis the protein is bound into units known as "keratin". After being synthesized, the proteins are gathered into fibrillar arrangements and then eventually lost with the desquamation of the stratum corneum.

Human epidermal protein reduplication can be measured by the use of a single radioactive amino acid.[11] It takes 28 days for the glycine-C^{14} label to be maximally detected in the proteins of the normal stratum corneum, while in psoriasis only four days are required. Thus, the epidermal turnover time in psoriasis is 7-8 times normal.

The protein which is synthesized in the basal layer of the epidermis forms tonofilaments. These tonofilaments are then aggregated further into tonofibrils. In the granular layer, the keratohyalin granules are synthesized. These granules are formed in the layer where nuclear degeneration occurs.[12] Nuclear degeneration causes the epidermal cells to become dry and compact. This process is accompanied by a release of methionine and an increase in the abundance of cystine as disulfide is formed from the sulfhydryl in the amino acids.[13] It is in this chemical reaction that certain drugs achieve their usefulness in treating psoriasis. Mercury, arsenic, and other heavy metals retard epidermal cell maturation by preventing the conversion of sulfhydryl compounds to disulfide. These metals act as reducing agents during this retarding process.

The stratum corneum varies between 15 and 37 layers of cells in hyperkeratotic psoriatic lesions.[14] The stratum corneum can be divided into three layers: a basal layer, an intermediate layer, and a superficial layer. The basal layer is 2-14 cells thick with each cell possessing dense cytoplasm. The cells are filled with densely arranged keratin fibrils. The intermediate layer is 9-17 cells thick and thus forms the main portion of the stratum corneum. The cells in this area are more opaque with fibrils and a nonfibrillar substance than the basal layer cells. The superficial layer is composed of 2-6 cells in thickness. The cytoplasm is even less opaque here.

ESTERASES - Esterases have been divided by Gomori[15] into two large subgroups: aliesterases and cholinesterases. The aliesterases are composed of nonspecific esterases and lipases. There is a remarkable degree of nonspecific esterase activity throughout the entire thickness of the parakeratotic lesions of psoriasis. This increased accumulation of esterases in the parakeratotic horny layer is attributed to the rapid keratinization process. Nonspecific esterase activity is evident in other dermatoses but not as much so as in psoriasis. On the other hand, it is felt that cholinesterase is markedly reduced around the papillary capillaries and in the epidermis of psoriatics.[4] A reduced decomposition of acetylcholine could explain the capillary dilation which occurs in psoriasis.

PHOSPHATASES - Phosphatases are another group of enzymes which have received extensive study. However, biochemical knowledge comes very slowly and much is still to be learned regarding these enzymes. One would expect to find alkaline phosphatase in every tissue of the body since the immediate source of energy for all cellular activity comes from the splitting of energy-rich phosphates. The test for alkaline phosphatase in the parakeratotic layer of psoriasis was nonspecific.[16] Evidently, keratinization does not depend on alkaline phosphatase. The cells of the epidermis do show acid phosphatase activity. The activity of acid phosphatase is particularly increased in the cells beneath the stratum corneum. This transitional zone probably houses a large store of hydrolytic enzymes to help in the decomposition of nuclei and cytoplasm. This is further borne out by the fact that the parakeratotic horny layer of psoriasis is very rich with regard to acid phosphatase activity. However, the behavior of acid phosphatase is not specific for psoriasis; it simply represents the accelerated rate of keratinization which can be found in

any condition with parakeratosis.

Beta-glucuronidase is also present in psoriatic epidermis. As the amount of acanthotic proliferation increases so does the concentration of this enzyme.[4] The function of this enzyme is not well known. It has a definite connection with cellular proliferation. Since it is found in high concentration in the parakeratotic horny layer, it must have a definite role in keratinization also. One of the best theories on the function of beta-glucuronidase is that it is a degradating agent of epithelial mucins.[4] After hyaluronidase acts upon hyaluronic acid to produce certain disaccharides, beta-glucuronidase degrades these disaccharides into monosaccharides.[17]

LIPIDS - The concentration of lipids present in psoriatic lesions is increased above that found in normal skin.[18] Phospholipids and unsaturated lipids are present not only in the transitional zone beneath the stratum corneum, where they are usually to be found, but also throughout the parakeratotic layer. Once again the high concentration of these lipids is explained by the rapid keratinization in psoriasis.

Blood lipids have been investigated in great detail in psoriasis. Much controversy surrounds the level of serum cholesterol in psoriasis, but more researchers feel it is increased than feel it is decreased. However, it appears that the more widespread the disease is, the lower the serum cholesterol becomes.[18]

DERMIS - The psoriatic dermis manifests several aberrations which are significant but not specific for this disease. The papillary region, the upper reticular layer, the basement membrane, the capillaries, the ground substance, and the connective tissues are the areas chiefly involved in the corium of a psoriatic.

The elongated papillae in psoriasis show a marked dilatation of the tortuous capillaries. This phenomenon has been known since 1926 when microscopic pictures were first obtained.[4] But dilatation by itself is not the only change found in the capillaries of the papillae. These capillaries also manifest a high concentration of alkaline phosphatase activity.[19] Periodically the amount of alkaline phosphatase is present in higher concentration in the endothelium of the arterial ascending limbs than in the descending capillary limbs.

The increased activity of alkaline phosphatase probably simply signifies a high degree of metabolic activity; although, it has been conjectured that the phenomenon is related to vascular permeability, and thus to the passage of substances through the capillary membrane.[20]

Phosphorylase activity is also found to be increased in the papillae capillaries. Again, this is probably just an indication of the high metabolic activity which is present in the endothelial cells.

The upper dermal layers are characterized by a metachromasia. The metachromasia indicates the presence of acid mucopolysaccharides.[21] The area of inflammatory infiltrates in the dermis has a marked accumulation of acid, nonmetachromatic(depolymerized) mucopolysaccharides. The increase in acid mucopolysaccharides is certainly not related to an increased production of ground substance. Ground substance is produced by fibroblasts, and the latter are not more numerous in psoriasis than in normal corium. Under normal circumstances, acid mucopolysaccharides are combined with proteins. In this combined form with proteins, the acid mucopolysaccharides do not react metachromatically since the acid groups necessary for this reaction are blocked by the combination. Protein degradation can split the protein-mucopolysaccharide linkage to free acid

mucopolysaccharides so they may become metachromatic. The marked zone of metachromasia in psoriasis is probably due to increased proteolytic activity in the corium. The aminopeptidase activity, especially that found in the lymphocytes, is quite high in the dermis and is one measure of the increased proteolytic activity that takes place there.[4]

The subject of psoriasis has certainly been studied in depth since Robert Willan's description in 1801. It has had more investigation than any other skin disease.[18] Carbohydrate metabolism is probably the best understood and most studied area in psoriatic biochemistry. Numerous assays have revealed considerable knowledge of enzyme systems. But as this paper shows, work in protein, lipid, phosphatase, esterase, and dermal biochemistry is also progressing at a steady pace. This paper also shows how much work and study is still required to fill the gap that exists in our understanding of psoriasis.

Psoriasis is like any other disease in medicine - just as one thinks he has begun to understand it, new developments and discoveries overshadow previous findings. The advent of finer assays, the use of electron microscopy, and the combined efforts of various specialists will be essential if the whole story of psoriasis is to be unraveled. As A. Tickner says, "For the biochemist without knowledge of dermatology is myopic but the investigative dermatologist without knowledge of biochemistry is impotent and his endeavours will be unfruitful."[18]

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