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ORIGINAL ARTICLES

THE ROLE OF SKIN CHEMISTRY IN THE UNDERSTANDING OF DISEASE MECHANISMS *

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Mr. President and Colleagues,

It is a privilege for me to be the guest speakar this evening. It is more so, because I have the opportunity of addressing a joint meeting with the Physicians and I find this a unique situation in India. It is not only unique but desirable in the interest of medicine in general to bring about such an integration of the different medical specialities. Dermatology is a legitimate child of internal medicine, and basic sciences of biochemistry and physiology have many common areas in both. My interest in dermatology has been fortified by my hobby of biochemistry, and today I wish to bring out some facets of the biochemical reactions in the skin which mirror the systemic background of body metabolism. Skin has many functions out of which protection against external noxious stimuli and regulation of permeability against many environmental physico-chemical substances are the most important. I wish to bring out (1) the biochemical mediations between the structures and functions of the skin and (2) to illustrate some disturbances in the skin brought about by specific metabolic disorders such as in phenylketonuria, Hartnup disease, porphyrinuria and diabetes in which diseases we have adequate knowledge which explains the exact mechanisms of these diseases.

Fig. 1. Summarises the mechanism of protection on which I am going to talk.

In this figure I have brought out some of the structures and functions of the skin to which I am going to restrict my remarks. The horny layer of the skin contains the substance keratin. This is developed by an intricate process of biogenesis of keratinisation starting at the basal layer of the epidermis and progressing through the rete malphigii and stratum granulosum. The end product of this process is the keratin which has to serve the function of total protection against the noxious stimuli and the permeation of physicochemical substances in either direction. This kearatin membrane resembles cellophane in appearance and

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transparency. Its thickness is less than one per cent of that of a single erythrocyte. This protection against permeability is in effect maintained by the integrity of the barrier zone which consists of a thin layer of cells. The fragility of this layer can be easily demonstrated by the stripping experiment. Stripping the skin about ten times is enough to damage the barrier function. When the barrier zone is removed, water loss from the underlying tissues would be the same as from an open water surface.

The basal layer of the epidermis contains melanocytes in between the basal cells. These are derived from the neural crest and their main function is to synthesize melanin by oxydation of tyrosine which is mediated by tyrosine oxydase through the products of DOPA. The biochemical intricacy of melanin production has been studied by several workers and it is not my intention to go into the details of this knowledge. The tyrosinemelanin synthesizing system has many checks and counter checks which activate or retard melanin production but ultra-violet radiation is its main activator. Melanin is injected in the basal cells and some of it drops down in the corium and is taken up by the macrophages which are then called the melanophores. Melanin is not a protection against ultra-violet radiation but a non-specific absorbing agent against all the wave lengths from infra-red to ultra-violet. Recently it has been shown that urocaninic acid which is formed from histidine in the stratum corneum has specific absorption properties for ultra-violet rays and this gives additional protection.

Going deeper in the dermis I shall bring out the biochemical background of inflammation clinically visible as erythema, wheals and oedema. The mast cells which are situated beside the capillaries, liberate histamine and related amines and heparin. The higher the number of mast cells, the stronger is the reactivity of the skin. The mast cells have granules which can be seen by metachromatic staining, and these granules contain the amines and heparin just mentioned. (see Fig. 1). The mast cells liberate the granules in the tissue under the influence of appropriate stimuli. The granules dissolve at once in the tissue liberating pharmacodynamic substances. These amines are generally bound by several systems which serve to limit the duration of their action. (Fig. 2). The bound amines can be split by the physicochemical milieu of the tissue such as the pH and the enzymes. The granules in the basophil leucocytes are also similar in nature and are liberated by a similar mechanism of degranulation. This reaction of degranulation can be specifically demonstrated in allergic reactions of the immediate type and is now used as an indicator of such specific allergic sensitivity. Another type of important inflammatory reaction to consider is the one of hypersensitivity to a foreign antigen. This is mediated by the antibodies which are formed in the reticulo-endothelium system and transported by the lymphocytes and the plasma cells. The antigen-antibody reaction takes place in the corium and results in inflammation. There is some evidence to suggest that this is brought about at least partially by histamine liberation from basophil leucocytes. The antibodies in this reaction are of the sessile type which are different from

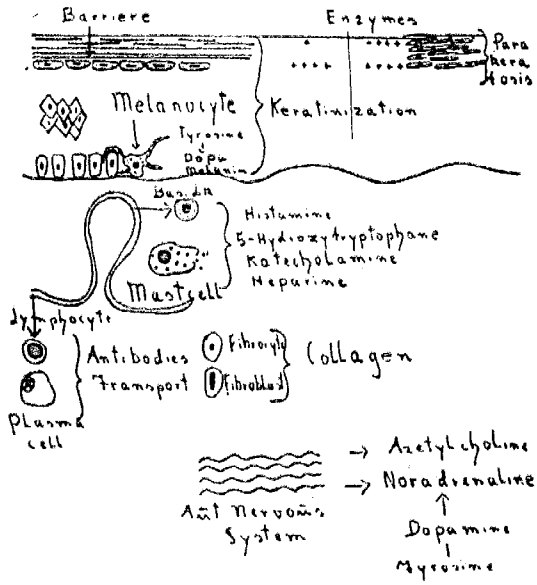

Fig. 1

Binding of Histamine

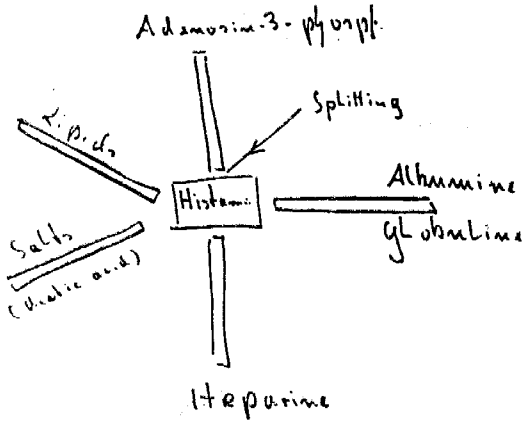

Fig. 2

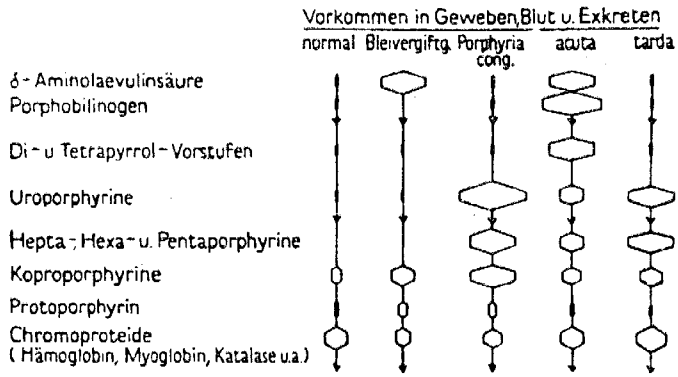

Abb. 29: Die Verteilung von Porphyrinen und Vorstufen

Fig. 3

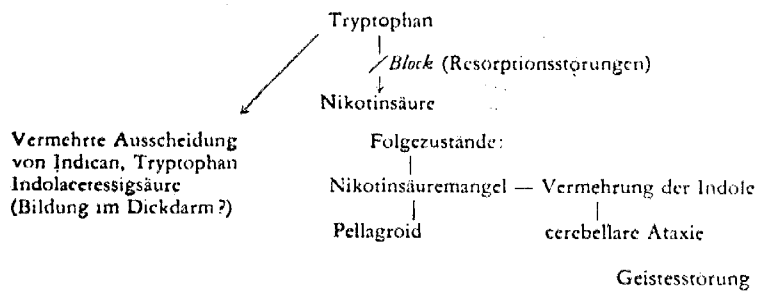

Abb. 26: Pathogenese der HARTNUP-Krankheit

Fig 4

those which mediate the immediate reaction provoked by the labile circulating antibodies demonstrable by passive transfer technique.

Although the physical function of collagen in preserving the elasticity of the skin is well-known, its physiological function is not well defined. Pathologically, however, it has been found that the collagen diseases result because of changes in the interfibrillary substances without visible damage to the fibres. Collagen itself originates from the secretory activity of the fibroblasts which also produce the precurser substance of the fibrils which later turns into fibres, by aggregation. A keloid may develop on the healing of a wound when the secretory activity of the fibroblasts continues for a longer time. Last but not the least important activity of the skin is mediated by the autonomic nervous system which liberates the noradrenaline through the adrenergic fibres and acetylcholine by the cholinergic fibres. The enzymology of this system has been extensively worked out and is the same as in the nervous system as a whole. The functions of this system are mainly concerned with sweat secretion, circulatory regulation and pilary erection. Lastly, interestingly it is brought out that the energy supply for the functions of a single epidermis cell does not differ from that of the other cells of the human organism. The pentose phosphate cycle which results in the production of di-and triphosphopyridinnucectides is the source of energy supply.

Next I shall bring out some systemic disorders of metabolism reflected on the skin. Although skin does not reflect many metabolic disorders, generally there are some situations in which it does so because of the distribution of biochemically active substances which originate from the wrong pathways and affect the skin in specific ways. Certain vitamins and amino acid deficiencies are reflected on the skin because these substances are necessary for the normal functions of the skin. As these disorders are more well-known to you in your country I shall not go into the details of these. I wish to bring out essential biochemical details of the disturbances of prophyurin metabolism which are not as well appreciated all over the world because of their rarity. But I believe from my experience that these diseases are not rare, but they are rarely diagnosed because the physicians generally do not think of looking for the porphyrins. The studies of literature show increasing number of reports of this disorder which confirms my belief. In the following diagram I have brought out the essential biochemical features of the different types of porphyrias. (Fig. 3). The clinical types of porphyria have been mentioned in various publications and hence I will not go into the details of these which are well-known to you. However, I wish to focus your attention on two features of the disease on which we have been working in our department. Although the skin shows localisation of symptoms mainly in the sun exposed areas, contrary to expectations, we did not find any specific increase in the ultra-violet sensitivity of the skin in Porphyria Congenita Erythropoetica and Porphyria Hepatic Chronica. In contrast to the natural porphyrins which I have shown you in the diagram, haematoporphyrin which is a synthetic compound

some time used in the treatment of mental disorders, has been shown to give rise to marked ultra-violet sensitizing potential. Although we have no knowledge of the missing link which may be responsible for the skin changes in the sun exposed areas, surely it is not a known porphyrin.

Another work carried out in our clinic has been on the disturbed iron metabolism in the hepatic porphyrin. When working on the problem of chronic hepatic porphyria, it was found that there is an excess of iron in the blood of the patient which is not metabolised to haemoglobin. This excess of iron is accumulated in the liver and other systems as in haemochromatosis. Besides the lack of metabolism of iron, it is also possible that more iron is reabsorbed through the intestinal mucosa than under normal conditions. By bleeding the patient of 500 ml. of blood twice a month, the iron content was sufficiently diminished to normal levels within four months. At the same time the skin manifestations also improved by this procedure.

During the last year a new type of porphyria was discovered by several teams of workers at the same time, and this has been named as the 'Familial protoporphyrinic Light Urticaria.' Its main features are the demonstration of porphyrins on the erythrocytes, and in the upper layers of the skin. On exposure to light, the patient develops urticaria within two minutes. It is only in this type of porphyria that a fluorescing and light senstising substance has been demonstrated in the skin, but the exact chemical composition of this substance is not yet defined. This disease is also characterised by amino-aciduria.

The next disease on which I shall talk is phenylketonuria in which there is a lack of activity of phenylalanin-hydroxylase. This results in blocking in the formation of tyrosine-a precursor of melanin-and this ultimately results in Albinism. In this disease, as a result of this blockage, phenylpyruvinic acid accumulates in the tissues and appears in urine. Accumilation of phenylalanine in the brain is also responsible for the symptoms of chorea which is a part of this syndrome.

Hartnup Disease is another interesting biochemically defined disease, in which there is an inhibition of resorption of tryptophane through the internal mucosa. (Fig. 4). As a consequence of this, there is lack of synthesis of nicotinic acid resulting in the pellagroid picture seen on the skin. There is also intoxication syndrome because of absorption of accumulated indols from the bowels. This synndrome can be corrected specifically by the use of nicotinamine and nicotinic acid.

Lastly, I wish to bring out some recent knowledge on the cellular defects occurring in diabetes as a result of lack of proper insulin action. It was not realised before, that the lack of insulin interferes with the permeability of the cell membrane with resultant lack of glucose transport to the cells. The sugar

level of the skin in diabetes is not high so as to explain the fungal and bacterial invasions. It may be that the infections result because of the possibility of utilization of non-metabolised sugar in the skin by the pathogenic organisms. By speaking on diabetes, it was not my intention to carry "Coal to Newcastle" or as a German I would like to say carry Beer to Bangalore," which I have enjoyed better than the German beer. I did so, only to emphasize the unity betweeen the legitimate child of dermatology with the parents of medicine for which I have presented additional biochemical evidences.