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Short Communication

Job Triptych: Typical Cutaneous Expression of An Immunodeficiency Disease

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In 1966, two girls with recurrent "cold" abscesses and eczema were described by Davis, Schaller, and Wedgwood in The Lancet [1]. "Cold" abscesses because the skin infections, a form of inflammation, didn't feel warm. Davis et al. wrote: " The pitiful appearance of these patients and the history of recurrent abscesses and skin infections makes the name " Job's syndrome " seem suitable." [1] There is (fortunately) an increasing trend in medicine to abandon eponyms, naming a disease after an (existing or fictitious) person [2-4], which is one of the reasons why Job's syndrome is now known as hyper IgE syndrome (HIES) [5]. HIES is defined by the triad of increased serum concentrations of IgE, dermatitis, and recurrent skin (and lung) infections. It should be noted that the original publication of Davis et al. doesn't mention elevated IgE [1] because the first description of this immunoglobulin class wasn't published until 7 months later in 1966 [6]. According to the chronology of The Bible, Job died more than 3000 years ago. His lifeline is special, even by Biblical standards. Job was a rich man, happily married, with ten children, and he was very religious. He was so religious that God himself boasted to the Devil how faithful Job was. The Devil challenged God to test Job's faith, and with God's approval, the Devil did so. The condition of the challenge was that Job himself had to stay alive. Within a day, all ten of Job's children were killed, along with his complete livestock and all his servants. Job, however, remained faithful to God. So, again with God's approval, the Devil devised something far worse: Job would be completely covered in pustules, which happened (Figure 1). The wife of Job considers her husband crazy for still keeping faith in God and leaves him. Now Job starts to have doubts, but in the end God decides that Job has suffered enough, heals him of his illness, and all of a sudden he has "new children". It could be that his seven sons and three daughters were brought back to life, the Bible is unclear about this. There is no mentioning of a "new" wife, but in any case, Job makes a full recovery and lives a long and happy life. What is most special about the story? That Job's skin infections, at least to God, to the Devil, and to Job and also to Job's wife, were apparently more important and a more severe punishment than the loss of his ten children.

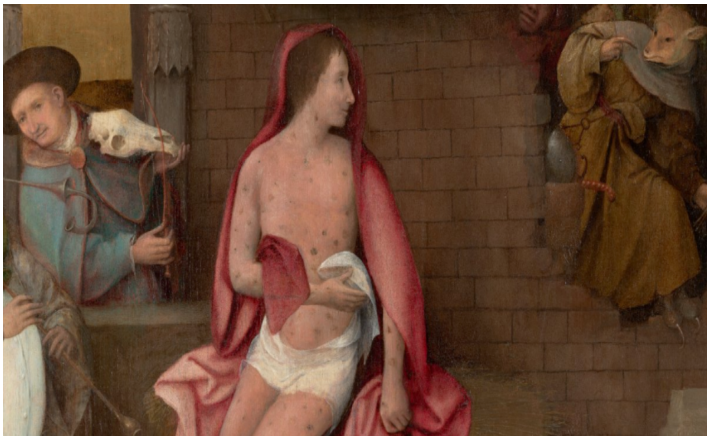

Figure 1: Detail of the middle panel of the Job Tryptych, (workshop of) Jheronymus Bosch, 1500-1540, Groeninge Museum, Bruges, Belgium. Source: https://commons.wikimedia.org/wiki/File:Triptych_of_Job_Bosch_Groeningemuseum_01052015_1.jpg Assessed January 5, 2023.

The clinical features of Job's syndrome, HIES, include eczema, which usually develops quite soon after birth, recurrent skin infections with *Staphylococcus aureus*, with formation of pustules, and recurrent pneumonia also caused by *Staphylococcus aureus* or a fungus. In addition, there may be skeletal abnormalities (scoliosis), dental abnormalities (retained primary teeth) and

connective tissue abnormalities [5]. HIES syndrome is caused by dominant negative variants in the STAT3 gene [7]. STAT3 (Signal Transduction and Activator of Transcription 3) is an important signaling molecule in the activation of cells of the immune system. Via a number of steps, not all of which are clearly understood, this leads to greatly increased concentrations of the IgE class of immunoglobulins and of eosinophilic granulocytes. The massive overproduction of IgE is likely the result of misdirection and regulation of the immune response [8]. Another consequence of the incorrect control is that Th17 cells are greatly reduced in patients with HIES [9]. Subsequently other genetic defects, in most cases in STAT3 associated molecules or in STAT3 signaling receptors, have been identified which can lead to an HIES phenotype, usually with a milder and more diverse clinical spectrum [10]. These include loss-of-function mutations in Zinc Finger Protein 341 (ZNF341) [11], Interleukin 6 Signal Transducer (IL6ST) [12], IL6 Receptor (IL6R) [13], Tyrosine kinase 2 (TYK2) [14], and Serine Peptidase Inhibitor Kazal Type 5 (SPINK5) [15]. Dominant negative mutations in Caspase Recruitment Domain-Containing Protein 11 (CARD11) [16] and IL6ST [17] also result in the clinical and immunological phenotype of HIES. There are more primary immunodeficiency diseases with elevated IgE such as Dedicator of cytokinesis 8 (DOCK8) [18], Phosphoglucomutase 3 (PGM3) [19], and Omenn syndrome [20], but they all have associated T-cell defects and therefore are not be classified as HIES [10]. The diverse genetic causes lead to a widening of the definition of HIES, with or without associated non-immune phenomena. It also shows how important strict regulation of each and every step in the (IL-6) inflammatory pathway is for maintaining homeostatic control of the immune system.

The treatment of Job's syndrome, as well as the other molecular causes of HIES, consists of prophylactic administration of antibiotics, appropriate skin care, and intravenous immunoglobulins. Of these three options, Job himself had only the proper skin care available. Despite this, his whole body remained covered with cold sores or their scars. As indicated above, the defective gene of Job's syndrome, STAT3, is primarily important for the functioning of the immune system. However, recent research (in mice) shows that STAT3 is also involved in the development of brain functions [21]. Perhaps that was why Job considered the cold sores on his own body a greater punishment from God than the death of all his ten children.

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