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Title: The Early History of the Eosinophil

Short title: Eosinophil history

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Conflict of Interest

The author declares no conflict of interest

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Summary

In 1879 Paul Ehrlich published his technique for staining blood films and his method for differential blood cell counting using coal tar dyes and mentions the eosinophil for the first time. Eosin is a bright red synthetic dye produced by the action of bromine on fluorescein and stains basic proteins due to its acidic nature. It was discovered in 1874 by Heinrich Caro, Director of the German chemical company Badische Anilin- und Soda-Fabrik. Ehrlich

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introduced the term “eosinophil” to describe cells with granules (which he called alpha-granules) having an affinity for eosin and other acid dyes. He also observed black-staining, indulinophilic, beta-granules in bone marrow-derived eosinophils which were probably immature crystalloid granules in eosinophil myelocytes. Ehrlich described the features of the alpha-granule and the cell’s distribution in various species and tissues. He speculated correctly that the alpha-granule contents were secretory products and described several causes of eosinophilia including asthma, various skin diseases, helminths and reactions to medications. However, the cell was almost certainly observed by others before Ehrlich. . In 1846 Thomas Wharton Jones (1808-1891) described “granule blood-cells” in the lamprey, frog, fowl, horse, elephant and man. He “borrowed” the term granule cell from Julius Vogel (1814-1880) who had observed similar cells in inflammatory exudates. Vogel in turn was aware of the work of the Gottlieb (Théophile) Gluge (1812-1898) who used the term “compound inflammatory globules” to describe cells in pus and serum. Almost 20 years before Ehrlich developed his staining methods, Max Johann Sigismund Schultze (1825 - 1874) performed functional experiments on coarse granular cells using a warm stage microscopic technique and showed they had amoeboid movement and phagocytic abilities. Although these early investigators recognised distinct granular cells Ehrlich’s use of stains was a landmark contribution which heralded modern studies on eosinophils and other blood leucocytes.

Introduction

Unravelling the secrets behind the formation, function and fate of the eosinophil has inspired (and perplexed) clinicians and scientists ever since it was unequivocally identified by Paul Ehrlich in the 1870’s. There is now a vast literature devoted to the cell and the number of eosinophil citations from PubMed has increased almost exponentially since the 1960’s. Eosinophils , unlike neutrophils, lymphocytes and monocytes, do not seem to play a vital physiological role in the sense that their removal or depletion, both in man and experimental animals, is not associated with any obvious deleterious effect. On the other hand their numbers are markedly increased in certain pathological conditions, particularly helminthic parasitic infections and atopic allergic disease (1). It is generally accepted that eosinophils play a poorly defined role in innate and adaptive host responses against selected pathogens and contribute to tissue damage in the hypereosinophilic syndromes and certain asthma

phenotypes. The central morphological feature of the cell is the presence of large intracytoplasmic granules (variously termed alpha-, specific- or crystalloid-granules) which contain several toxic basic proteins. It is the capacity of these cationic granule proteins to bind acid, aniline dyes, particularly eosin, which led to Ehrlich's seminal discovery. This article summarises Ehrlich's contributions and some of the events leading up to it.

Early descriptions of granulated cells

The first description of leukocytes was reported simultaneously in 1843 by Gabriel Andrai (1797-1878) and William Addison (1802-1881) (2). This was almost 200 hundred years after Jan Swammerdam (1623) first identified the red cell using a compound microscope in 1658. Andrai and Addison both concluded that red and white blood corpuscles were altered in disease and Addison speculated that pus cells were blood leucocytes which had passed through the wall of the blood capillaries. There was much speculation at the time as to whether pus cells were formed locally or derived from the circulation. It was noted that, occasionally, pus cells were found together with cells containing granules.

One of the earliest, if not the first, description of "granule cells" in inflammatory exudates was made by the Belgium clinician and scientist **Gottlieb (Théophile) Gluge** (1812-1898) (Fig 1) (3). Gluge was a pioneer medical researcher and personal physician to the King of Belgium. He was one of the first clinicians to examine diseased tissue microscopically. His major work was the "Atlas der Pathologischen Anatomie (1843)" in which he described "inflammatory globules", a term he preferred to "granular cells". These cells were observed not only in inflammatory exudates but also in colostrum and the ovary and resemble eosinophils (Fig 2). Gluge believed that his inflammation corpuscles were derived from precursor material by a "second mode of cell formation" in which "small bodies appear" which "resemble fat granules... but also frequently may consist of protein or sometimes of pigment. These (granules) average in size from 1/500 to 1/400 of a millimetre in diameter, and become associated, in groups of from 10-40 or more...the groups of granules are mulberry-like globules, measuring on average 1/30 of a millimetre, and in this condition are frequently observed". In one illustration Gluge describes "Stasis and metamorphosis of blood corpuscles into inflammation-corpuscles". The drawing shows eosinophil-like cells

(his “inflammation globules”), probable red cells and empty cells (neutrophils?) together with venous stasis. Taken together his various drawings of inflammation globules, which he believed essentially were large pus cells containing fat droplets, have the appearance of intact and partially degranulated eosinophils. I am unaware of any previous documentation of granular, eosinophil-like cells.

Gluges work was recognised and extended by the eminent pathologist **Julius Vogel (1814-1880)** (Fig 1). Vogel was a skilful microscopist and an expert in basic sciences. He was the Professor of Pathology at Göttingen, Germany, and published his pioneering book (also in 1843) on the “Pathological Anatomy of the Human Body” (Fig 3) (4). It was the first comprehensive general pathology book and contained numerous macroscopic and microscopic illustrations. The book was remarkable in that the bulk of the figures showed, for the first time, microscopic features of specific pathologic lesions (Fig 2). It was rapidly translated from German into English and was published in London and Philadelphia in 1847. Among the illustrations are cytological preparations of sputum and pleural and pericardial effusions of patients with bronchitis, tracheitis and pneumonia. In these Vogel described numerous granular cells which “are for the most part round, but sometimes elongated or even angular...it is difficult to distinguish whether they (the granules) are on the surface or in the interior of the cell”. Vogel believed that the granules consisted of fat (olein and margarin) since they dissolved in organic solvents. He also wrote “when the granular cells have attained their full development, the cell-wall disappears, and the granules contained in the interior are liberated, and form larger and smaller heaps”. The illustrations show cells with the clear morphological characteristics of eosinophils, both intact and in various stages of degranulation.

Another convincing and comprehensive morphological “pre-Ehrlich” study of granular blood cells was by the British physiologist and ophthalmologist, **Thomas Wharton Jones (1808-1891)** (Fig 4). Wharton Jones studied medicine in Edinburgh and for a few years was the assistant to the anatomist Robert Knox.

(Footnote: While working for Knox, Wharton Jones purchased a body from William Hare on Knox's behalf, paying £7 10s to Hare. Jones thus became caught up in the scandal surrounding the notorious body-snatchers Burke and Hare, but was cleared by the investigating committee (*Obituary of Thomas Wharton Jones, The Lancet (1891) 1256-1258*))

He left Edinburgh for Glasgow where he studied ophthalmology and eventually settled in London, first as a lecturer at the Charing Cross Hospital and then as the Professor of Ophthalmic Medicine at University College. He had a special interest in inflammation and the vasculature and in 1846 published “The blood corpuscle considered in its different phases of development in the animal series” (5). In this article he described “finely granular and coarse granular blood-cells” in large number of species including the lamprey, frog, fowl, horse, elephant and man (Fig 5). He speculated incorrectly that the coarse granular cells were a stage in development of the finely granular cells. The blood specimens were treated with water or dilute acetic acid in an attempt to distend the cell. This naturally dissolved the intracellular granules but nevertheless his colour drawings show clearly, particularly in higher mammals, that the coarsely granular cells had the typical appearance of eosinophils. Even with primitive optics (a Ross compound microscope with a one eighth inch objective) he was able to estimate the diameter of the coarse granule to be $1/25,000^{\text{th}}$ of an inch.

Several years after the description of granulated cells by Wharton Jones, Vogel and Gluge, but almost 20 years before Ehrlich developed his staining methods, **Max Johann Sigismund Schultze** (1825 -1874) (Fig 4) performed functional experiments on coarse granular cells (which were almost certainly eosinophils) . Schultze was a distinguished German microscopic anatomist who was noted for his work on cell theory. He had studied medicine at Greifswald and Berlin and was appointed extraordinary professor at Halle in 1854 and, later as professor of anatomy and histology and director of the Anatomical Institute at Bonn. In his study, published in 1865 (“The heated stage and its use in the investigation of the blood”) he described, for the first time, four different types of leucocyte which we now recognise as the monocyte, lymphocyte, neutrophil and eosinophil (6). With his warm stage microscope he established that finely granular and coarsely granular human white blood cells moved and phagocytosed small particles (Fig 6). His illustrations and descriptions of movement leave little doubt that these finely and coarsely granulated cells were neutrophils and eosinophils , respectively. He writes “If one increases the temperature to that of the body a much quicker movement (of coarse granular white cells) develops with striking changes in form and a more

rapid amoeba-like movement develops with movement from place to place as we have just described in the finely granular white cell". He then went on to add particulate matter such as dyes and milk to the cell preparation and observed that "The coarsely granular white cells do take up granules of dyes as I have observed with aniline blue, amongst others. It was striking to me that the liveliness of the movement (of the coarse granular cells) was obviously much reduced following the uptake of dye particles, an appearance that I often met with the finely granular cells". According to Douglas Brewster (7) "the work of Scultze was more important than that of Ehrlich: not only did he distinguish four different types of white cells, but he demonstrated important differences in their movement and phagocytic abilities".

The story of Eosin

The founding father of the synthetic dye industry was an Englishman, William Perkin (1838-1907) (Fig 7) who at the early age of 15 years entered the Royal College of Chemistry (now part of Imperial College, London). His project was to extract quinine, much in demand at the time for treating malaria, from coal tar but in the process accidentally discovered aniline purple (mauve or mauveine) (8). Mauveine was a huge commercial success, particularly as a dye for silks and other fabrics. He then developed a method for producing the brilliant red dye alizarin from anthracene. Unfortunately for Perkin the German chemical company Badische Anilin- und Soda-Fabrik (BASF) patented the same process one day before he did and over the years he found his research and development efforts increasingly eclipsed by the German chemical industry.

The discovery of eosin is attributed to **Heinrich Caro (1834-1910)** (Fig 7), who was mentored by William Perkin and who returned to Berlin in 1866 to become Director of the BASF laboratory (Fig 8) (9). Caro had studied dyeing at the *Gewerbeinstitut* and chemistry at the University of Berlin. Caro enhanced William Henry Perkin's technique for deriving mauve dye from aniline and was made a partner in the firm. He also developed induline, Bismarck brown and Martius yellow. Caro's research also helped to define the structure of triphenylmethane, the parent compound of rosaniline dyes (used in Ehrlich's initial experiments). Caro discovered eosin (fluorescent red) in 1874 by adding bromine to fluorescein. Fluorescein had been discovered by Adolf von Baeyer and, in further

collaboration with Baeyer, Caro also developed methylene blue. Heinrich Caro was responsible for more of Germany's successes in the dye industry than any other individual. He died in Dresden in 1910.

(Footnote: The word eosin is derived from Eos the Titan goddess of the dawn and described by Nonnus of Panopolis as opening the gates of heaven with rosy fingers and golden arms so that Helios, her brother, could ride his chariot across the sky every day. In his adolescence Heinrich Caro was friendly with a young lady called Anna Peters, who, because of her industry was nicknamed "rosenfingrige Eos".

(Footnote: Eosin is a popular pigment with artists although eventual fading of the brilliant red colour over months and years is problematic. For example geranium lake (eosin plus alum) was used in abundance by Van Gogh (e.g. The Bedroom, Madame Roulin rocking the cradle). The beautiful violet-purple hue used to depict the walls of his room in Arles was made by mixing cobalt blue and white with geranium lake. The red in the purple paint has faded prematurely, probably even during van Gogh's lifetime, and left behind only the blue with which it had been mixed).

Paul Ehrlich (1854-1915)

Paul Ehrlich was a monumental figure in the fields of immunology, haematology, oncology and chemotherapy (Fig 9, 10). His childhood was not especially remarkable. He was the son of a distiller but his mother's cousin was the famous pathologist, Carl Weigert who inspired Ehrlich in the staining of microscopic tissue sections (11). As was the custom Ehrlich attended many universities and after graduation became assistant physician to Professor Frerichs at the Charite Hospital in Berlin. From the outset his heart was in research although he managed a heavy clinical load. Professor Frerichs was highly supportive of Paul Ehrlich and recognised his exceptional gifts. Tragically Frerich committed suicide in 1885 and was succeeded by Professor Gerhardt who was unsympathetic to Ehrlich's research. Added to this Ehrlich developed a persistent cough and found tubercle bacilli in his own sputum. He and his wife went to recuperate in Italy and Egypt but on his return to Berlin in 1889 he was essentially out of job. With help from his wife's parents he set up his own laboratory in an apartment until Robert Koch secured a post for him at Moabit Hospital in Berlin. In 1899 Ehrlich moved to Frankfurt am Main to the Institute of Experimental Therapy (*Institut für experimentelle Therapie*) and in 1906 he became the director of the Georg Speyer House in Frankfurt, a private research foundation affiliated with his institute. In 1908 Ehrlich

shared the Nobel prize in Physiology and Medicine with Ilya Mechnikov for their contributions to immunology.

As described by Hirsh and Hirsh (11) in their excellent account of the discovery of the eosinophil, Ehrlich's interest in the staining properties of dyes originated in his days as a medical student in Leipzig, where, in 1878 he submitted his dissertation on the use of aniline dyes for staining microscopic specimens (12). He obtained the dyes from his pharmacist friend, Herr Frank. The earliest experiments were with tissue sections where he experimented with the dye dahlia (monophenyl rosaniline). At first the results were unsatisfactory because he only managed to achieve diffuse, patchy staining of the cells. However, when he reduced the staining with dilute acetic acid ("decolourization") this produced intense blue-violet nuclear staining. He also observed that, with certain cell-types such as plasma cells (discovered by his mentor Heinrich von Waldeyer-Hartz (1836-1921)) there was staining of the cytoplasmic granules. Ehrlich became fascinated with the concept of cytoplasmic "granulation" but realised it was important to distinguish true cytoplasmic granules from artifactual aggregates of cytoplasmic material. Using basic aniline dyes he was able to demonstrate that various connective tissue cells appeared to be packed with acidic granules and so he proposed the name "mast cell" (from the German "masten" meaning to fatten or force-feed) (12). He then turned his attention to the staining of blood cells with dyes. This was initially difficult since the chemical fixatives used at the time destroyed intracellular granules. However Ehrlich was to develop a simple heating and air-drying method of fixation, which, together with use of acidic and basic coal tar dyes, lead to the discovery not only of the eosinophil, but the neutrophil, basophil and lymphocyte (Fig 10).

Curiously the first published work on the eosinophil ("Contribution to Knowledge of Granulated Connective Tissue Cells and of Eosinophil Leukocytes") did not mention the cell at all (13). The article was based on Paul Ehrlich's presentation to the Physiological Society of Berlin on January 17th, 1879 and so it is assumed that the section on the eosinophil had been deleted. It remains a mystery as to what Ehrlich actually said about the cell in this lecture. It is in his next paper ("About the Specific Granulations of the Blood"), also based on a presentation to the Physiological Society of Berlin in 1879, that the eosinophil is mentioned for the first time (Fig 9) (14). When discussing granule types in the white cells of vertebrates

he writes “The most important of these granulations by far is the eosinophil or alpha granulation, about which I have already spoken before this society on the 17th January of this year. These alpha granules are characterised by their affinity for a wide range of acid coal tar dyes”.

Ehrlich not only identified the eosinophil but he described many of its features in details and speculated, to the most part correctly, on its formation and function. For example he noted that the alpha granules (more commonly referred to now as specific or crystalloid granules) were either round, or had the shape of short rods with rounded ends and that there was variation in the number of nuclear lobes and that the number of granules fluctuates from cell to cell. Ehrlich observed eosinophils in all species of animals he studied and showed that there were large numbers in the bone marrow and suggested that this was the site of their formation. Moreover he noticed a second type of granule in these bone-marrow-derived eosinophils which stained black with an eosin-indulin-glycerin stain. He called these “beta granules” and thought they probably represented a developmental stage in the formation of alpha granules. It would be reasonable to speculate that the beta-granules were immature crystalloid granules (sometimes called primary granules) which are well documented in eosinophil myelocytes and appear blue or purple with differential stains such as Giemsa. ,

The eosinophil appears to have been a relatively small part of Ehrlich’s overall scientific focus. After its discovery at the beginning of his career he did not to return to the subject for about 20 years. At a lecture he gave in 1900 at an International Congress of Medicine in Paris he speculated that leukocyte granules were secretory products and “extruded by the protoplasm which contained them” (15). He also suggested that “the phenomenon of eosinophilia is dependent on the circulation of a substance which has a chemotactic action on eosinophils , and which serves to release preformed eosinophils from the bone marrow into the blood”. Thus Ehrlich described the cell and the staining properties of its granules, studied its distribution in various species and tissues as well as its morphology and formation in the bone marrow, and, speculated correctly that the granule contents were secretory products. He studied the distribution of the cell in various species and in tissues and commented on the physiological aspects of the composition of the granule. He also described various causes of eosinophilia (i.e. asthma, various skin diseases, helminths, post-febrile states, malignant

tumours as well as reactions to medications). Ehrlich also considered that myeloid and lymphocyte development was separate.

Legends to Figures

Figure 1

Gottlieb Gluge (possibly the first to describe granular cells-which he referred to as “inflammatory globules”) and Julius Vogel (who made extensive drawings of granular cells in inflammatory exudates).

Figure 2

Gluges “Atlas of Pathological Histology” (1847) translated by Joseph Leidy in 1853 (Left). Gluge proposed that blood corpuscles “metamorphosed” into inflammation globules. The cells shown in the upper right panel were believed to represent stages in this process. However they have the appearance of intact or degranulated eosinophils. Further examples of Gluges “inflammation corpuscles” are shown in the right middle and lower panels.

Figure 3

Vogels famous “Pathological Anatomy of the Human Body” translated by George Day in 1847. (left panel). The right upper and lower panel are examples of Vogels “pus corpuscles, which he also refers to as “granular cells” or “Gluge’s compound inflammatory globules”. They bear a striking resemblance to eosinophils.

Figure 4

Thomas Wharton Jones (who made an extensive study of granular cells in a wide variety of species) and Max Schultze (who performed functional studies on finely and coarsely granular cells)

Figure 5

Wharton Jones' coarsely granular cells in the blood of humans, horse and the elephant. The figures show his original drawings and captions from his 1846 paper (5).

Figure 6

The finely and coarsely granular white cells of Max Schultze taken from his 1865 paper. The cells were observed on a warm stage at 38⁰ C. The captions are from Douglas Brewster's translation (7).

Figure 7

William Perkin (the founding father of the synthetic dye industry) and Heinrich Caro (pupil of Perkin who discovered eosin)

Figure 8

The form of eosin commonly used in tissue staining is eosin Y (a and b). After its discovery in 1871 it was immediately successful as a fabric dye (c). Caro also discovered methylene blue (with Adolf von Baeyer) (d) and was Director of the Laboratory of the famous German chemical company Badische Anilin- und Soda-Fabrik (BASF) in Stuttgart.

Figure 9

Paul Ehrlich in 1878 (from Hirsh and Hirsh (11)). The first description of the eosinophil appeared in the *Archive für Anatomie und Physiologie* in 1879.

Figure 10

Paul Ehrlich in 1908. The coloured plate is from “The Histology of the Blood” by Ehrlich and Lazarus published in 1900. Triacid (orange G, acid fuchsin, and methyl green) was used as a differential leucocyte stain.

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Fig 1



Gottlieb Gluge
(1812-1898)



Julius Vogel
(1814-1880)

Fig 2

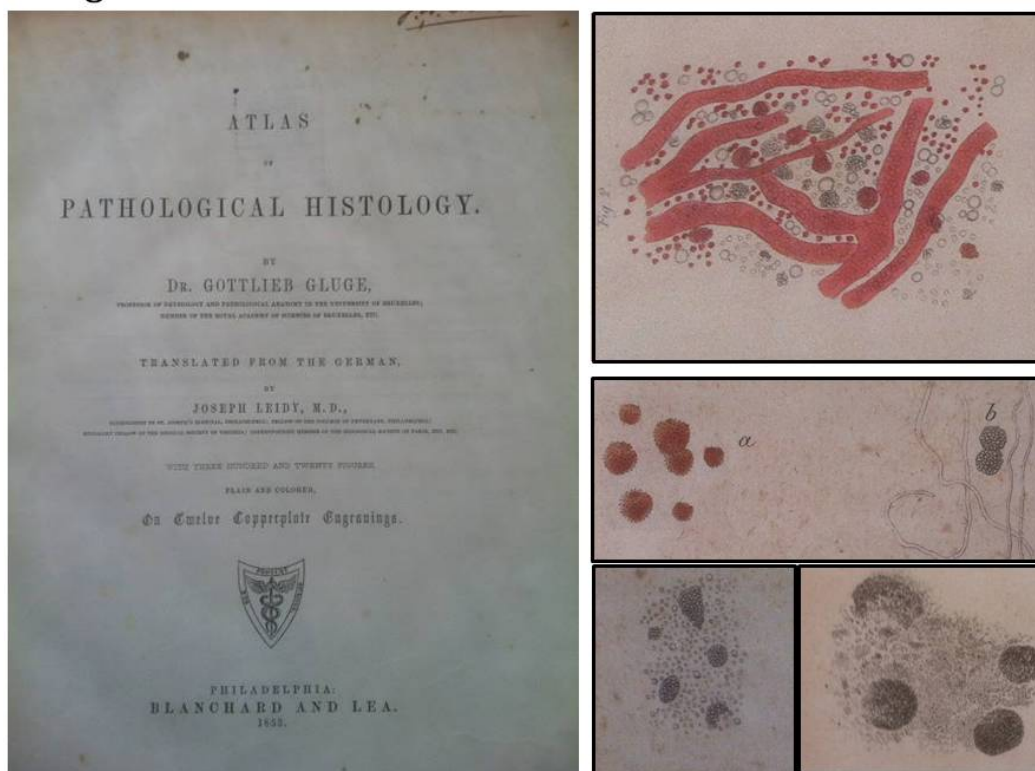


Fig 3

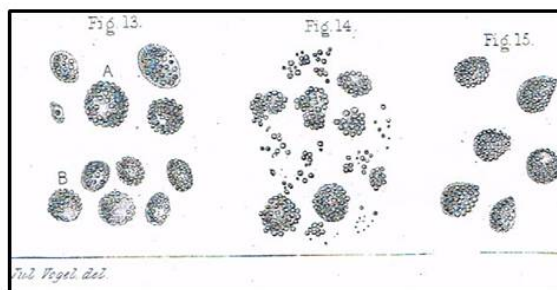
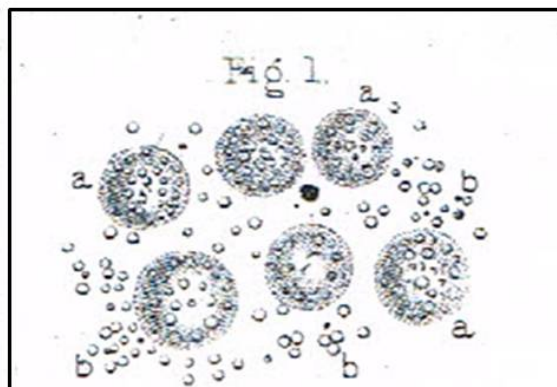
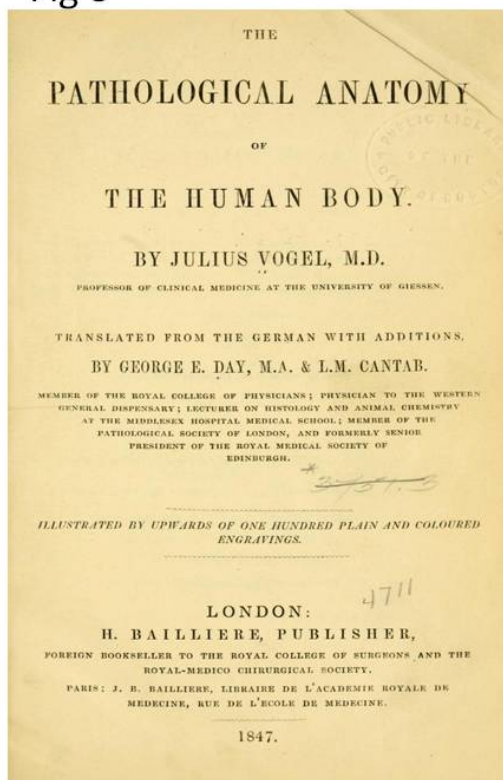
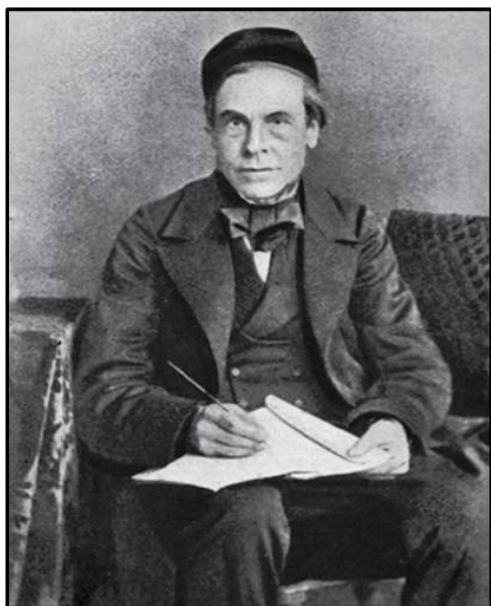


Fig 4



Thomas Wharton Jones
(1808-1891)



Max Schultze
(1825-1874)

Fig 5

- Fig. 1 a. The granule-cell of human blood in its coarsely granular stage distended by water.
 Fig. 1 b. The same, after being acted on by acetic acid. The granules have been dissolved and a single cellæform nucleus disclosed.
 Fig. 2 a. The granule-cell of human blood in its finely granular stage in a state of collapse.
 Fig. 2 b. The same, distended by water.
 Fig. 3 a. The granule-cell, coarsely granular stage, of the blood of the Horse.
 Fig. 3 b. The same, after being acted on by acetic acid.
 Fig. 4. The granule-cell, finely granular stage, of the blood of the Horse.
 Fig. 5 a. The granule-cell, coarsely granular stage, of the blood of the Elephant.
 Fig. 5 b. The same, in process of being acted on by acetic acid.
 Fig. 6. The granule-cell, finely granular stage, of the blood of the Elephant.

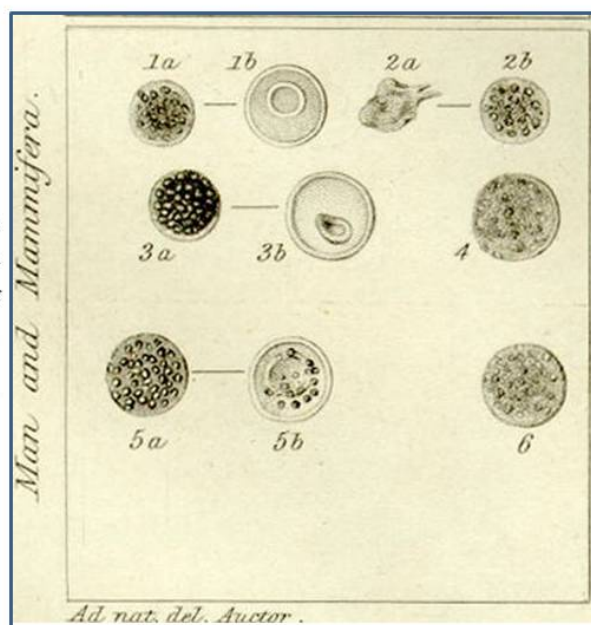
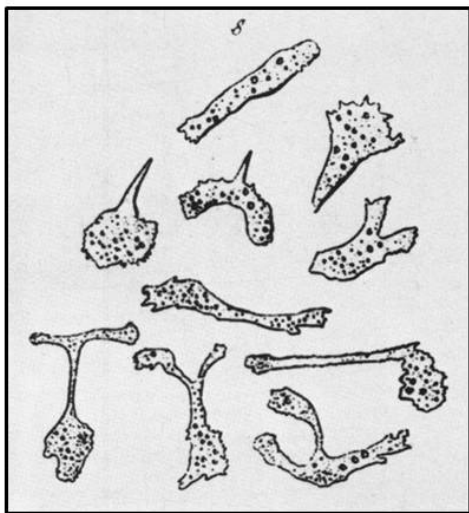
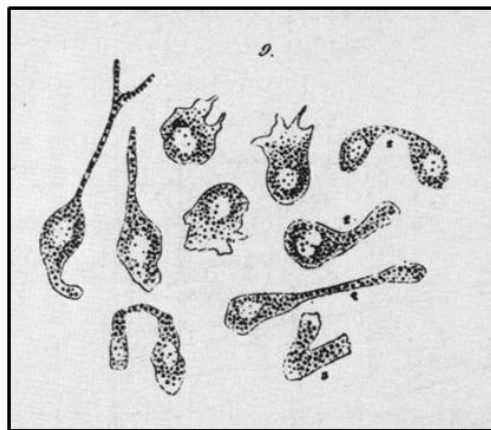


Fig 6

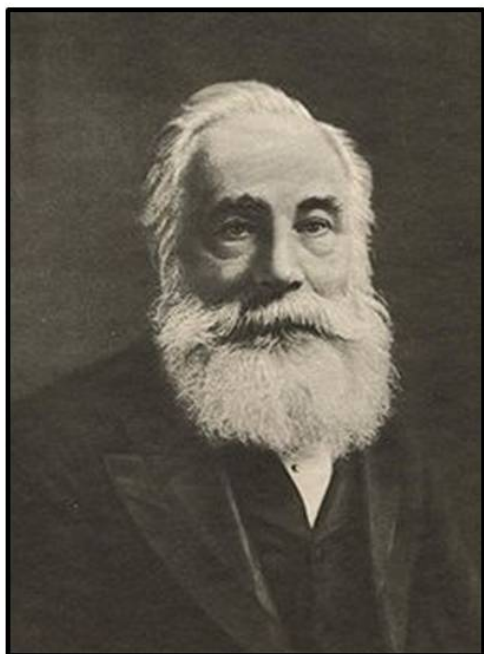


A finely granular white cell at 38° C on the warm stage, showing lively creeping movement. The shapes drawn show the same cell in a series of rapid changes in shape following one after another (Schultze, Fig. 8).



Coarsely granular white cells drawn in creeping motion at 38°C. The unnumbered cell with one nucleus and the cell numbered 2, with two nuclei, show successive changes in each of two different cells (Schultze, Fig. 9).

Fig 7



William Perkin
(1838-1907)



Heinrich Caro
(1834-1910)

Fig 8

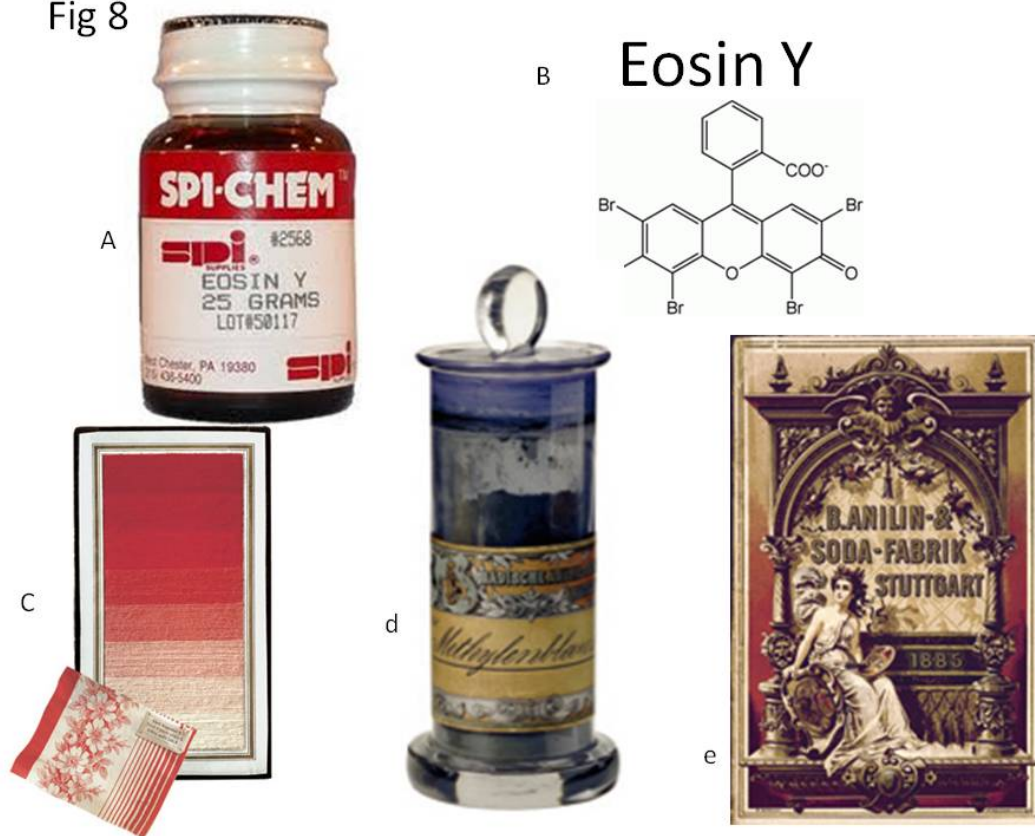


Fig 9



Über die specifischen Granulationen des Blutes*
P. EHRLICH

Die bei Weitem wichtigste dieser Körnungen ist die eosinophile oder α -Granulation, über welche ich schon am 17. Januar d. J. vor der Gesellschaft berichten konnte.* Die α -Granulation ist durch ihre Verwandtschaft zu der grossen Reihe der *sauren* Theerfarbstoffe charakterisirt, d. h. solchen, in denen wie im picrinsauren Ammon das färbende Princip eine Säure darstellt. Die Farbstoffe zerfallen, entsprechend

Fig 10

