South African Medical Journal
Suid-Afrikaanse Tydskrif vir Geneeskunde

VAN DIE REDAKSIE

DIE VORMING VAN ROOI BLOEDLIGGAAMPIES

William B. Castle, bekend vir sy oorspronklike werk oor die ,*intrinsic factor—extrinsic factor*' met betrekking tot kwaadaardige bloedarmoede, het onlangs ons huidige kennis van eritropoïese[1] in oorsig geneem.

Die vorming van rooi bloedliggaampies behels in hoofsaak die vervaardiging en verpakking van hemoglobien, maar die verskil in rooi bloedliggaampies tydens verskillende patologiese toestande dui aan dat die produksie van rooi bloedliggaampies en hemoglobien nie altyd op dieselfde skaal geskied nie. Normaal word 'n kritiese kontrole uitgeoefen maar tydens siekte kan die prosesse gewysig word.

By volwassenes kan aktiewe beenmurg op 3 maniere uitsit: deur die vetterige murg te verdring, deur die omliggende beenskors te verdring en deur vermeerdering van die getal eritropoïetiese selle; by kinders met kroniese hemolitiese bloedarmoede kan radioloë die verdunning van die skors van die lang bene en die ,hair-on-end'-voorkoms van die skedel uitken. Die groei en verdeling van selle is by die eritropoïese-proses in die beenmurg betrokke. Beenmurgpreparate toon mitoses op alle stadiums van sel-ontwikkeling, maar dit skyn asof die finale omskepping van normoblast in retikulosiet 'n postmitotiese proses is waarin die piknotiese kern eenvoudig weggewerp word. Die retikulosiet is die onmiddellike voorloper van die volwasse rooi bloedliggaampie.

Die jong eritropoïetiese selle, wat basofiliese kleuring toon ná gebruik van gewone kleurstowwe, bevat ribose nukleotides. Soos die globien (van die hemoglobien) in die sitoplasma begin vorm, kan polichromatofilie bespeur word. Die rypwording van eritropoïese selle in die beenmurg geskied in minder as 10 dae; dit word gestaaf deur studies van die murg ná hewige bloedstortings, deur die reaksie van kwaadaardige bloedarmoede tot geneeskundige behandeling, die herstel ná krisisse in aangebore hemolitiese geelsug en deur navorsing wat met radio-aktiewe isotope gedoen is.

Normaal bestaan die rooi bloedliggaampie in die perifeerbloed vir 100 tot 120 dae en soos dit bros word, word dit uiteindelik vernietig. Op enige hemoglobienstadium bly die toestand bestendig as eweveel rooi bloedliggaampies vervaardig en vernietig word. Sonder die stimulus van bloedarmoede kan normale eritropoïese vermoedelik nie aangewakker word nie, en, behalwe in die geval van polisitemie, kan die produksie van rooi bloedliggaampies nie aanmerklik verhoog word

EDITORIAL

ERYTHROPOIESIS

William B. Castle, well known for his original work on 'intrinsic factor—extrinsic factor' in relation to pernicious anaemia, has recently reviewed our present knowledge on erythropoiesis.[1]

The making of red blood cells consists essentially in the production and packaging of haemoglobin, but the differences in circulating red cells in various pathological states indicate that the formation of red cells and the production of haemoglobin do not always proceed at the same rate. Normally there is critical control but in disease there may be differences in the processes.

In the adult the active bone-marrow has the capacity to increase its size in three ways: by encroaching on the fatty marrow, by an increase in the number of erythropoietic cells, and by encroaching on the surrounding bone cortex; radiologists can recognize the thinning of the cortex of the long bones and the 'hair-on-end' appearance of the skull in chronic haemolytic anaemias of childhood. The process of erythropoiesis in bone-marrow involves growth and division of cells. Bone-marrow preparations show mitoses at all levels of cell differentiation, but the final conversion of normoblast to the reticulocyte appears to be a post-mitotic process in which the pyknotic nucleus is simply discarded. The reticulocyte is the immediate precursor of the adult red cell.

The early erythropoietic cells (young erythroid cells), which show the basophilic staining with ordinary stains, contain ribose nucleotides. As the globin of haemoglobin begins to form in the cytoplasm polychromatophilia is apparent. Maturation of the erythropoietic cells in the bone-marrow occurs in less than 10 days, as shown by studies of the marrow after severe haemorrhage, the response to therapy in pernicious anaemia, the recovery from crises in congential haemolytic jaundice, and studies with radio-active isotopes.

The red cell normally survives in the peripheral blood for 100-120 days. Eventually it becomes destroyed as it becomes fragile. A steady state exists at any haemonie tensy die konsentrasie hemoglobien in omloop aanmerklik daal. 'n Vermindering in die hoeveelheid suurstof in die slagaarbloed lei tot 'n verhoogde produksie van rooi bloedliggaampies. Afgesien van sulke vanselfsprekende oorsake van suurstofgebrek in die bloed soos die verlies of vernietiging van rooi bloedliggaampies, hoogte, hart- of longkwale, kan die toename in eritropoïese te wyte aan kobalt miskien toegeskryf word aan komplekse wat dit met suurstof vorm. 'n Verhoging in die hoeveelheid of die spanning van suurstof het die teenoorgestelde uitwerking. Dit is derhalwe nie die getal rooi bloedliggaampies nie maar die hoeveelheid hemoglobien in omloop—wat in noue verband met suurstofspanning staan—wat eritropoïese beheer. Die hemoglobienkonsentrasie bepaal waarskynlik die hoeveelheid suurstof wat gewoonweg die beenmurg bereik, maar afgesien van die stimulus van slagaar-suurstofgebrek, is daar rede om aan te neem dat vloeistof 'n indirekte invloed op eritropoïese uitoefen. Die milt het ook een of ander direkte of indirekte uitwerking op eritropoïese.

Fisiologiese en patologiese veranderings in eritropoïese gee aanleiding tot die produksie van rooi bloedliggaampies met abnormale grootte, kleur en vorm. Castle bespreek die eienskappe van sulke selle, en skenk volle aandag aan die probleme van abnormale eritropoïese. Die steurings wat volg op voedingsgebrek, buislose kliergebrek, vergiftiging van uitwendige of inwendige oorsprong en meganiese inmenging met die werking van die beenmurg, lei tot bloedarmoede as gevolg van die verswakte aktiwiteit van die beenmurg. 'n Paar spesifieke voedingstekorte kan die oorsaak wees dat eritropoïese by die mens nie tred hou met die normale vernietigingsproses van die rooi bloedliggaampies nie. Giftige stowwe kan eritropoïese, of een of ander ontgiftigingsmeganisme in die lewer, benadeel met die gevolg dat die beenmurg gewoonlik te veel eerder as te min selle bevat; sommige van die onvolgroeide selle kan miskien soos die megaloblasts van kwaadaardige bloedarmoede lyk.

Die oorspronklike werk bevat 'n uitstekende en volledig gedokumenteerde verslag oor eritropoïese.

1. Castle, W. B. (1954): Bull. N.Y. Acad. Med., **30**, 827.

globin level when red-cell production equals destruction. Presumably no increase above the normal rate of erythropoiesis can occur without the stimulus of anaemia and, except in polycythaemia, a marked increase in red-cell production cannot occur unless there is a marked reduction in the concentration of circulating haemoglobin. It has been shown that the stimulus to increased red-cell production is a reduction in the amount of oxygen in the arterial blood. It is interesting that apart from such obvious causes of anoxia as red-cell loss or destruction, altitude and heart or lung disease, the increased erythropoiesis produced by cobalt may be due to complexes it forms with oxygen. Increase in the amount or tension of oxygen has the opposite effect. Thus erythropoiesis is controlled not by the number of red cells but by the amount of circulating haemoglobin, which is closely related to oxygen tension. Normally the haemoglobin concentration would appear to determine the amount of oxygen brought to the bone-marrow but, apart from the stimulus of arterial anoxia, there is good evidence for an indirect humoral effect on erythropoiesis. The spleen also has some direct or indirect influence on erythropoiesis.

Physiological and pathological alterations in erythropoiesis result in the production of red cells of abnormal size, colour, and shape. Castle discusses the features of such cells, and fully considers the problems of abnormal erythropoiesis. The disturbances produced by nutritional deficiency, endocrine deficiency, intoxicants of external or internal origin, and mechanical interference with bone-marrow function, cause anaemia from hypo-activity of the bone-marrow. A few specific nutritional deficiencies cause erythropoiesis in man to lag behind the normal rate of red-cell destruction. Toxic substances may impair erythropoiesis or some detoxifying mechanism, perhaps in the liver, resulting in a bone-marrow which is more commonly hypercellular than hypocellular; some of the immature cells may resemble the megaloblasts of pernicious anaemia.

The original review must be consulted for an excellent and fully documented account of erythropoiesis.

1. Castle, W. B. (1954): Bull. N.Y. Acad. Med., **30**, 827.

CRYSTALS

A typical crystal is regularly geometric in its form, with sharp edges and plane surfaces. The regular outer form is due to a regular aggregation of smaller units having a uniform geometrical shape. This internal arrangement of the smaller units is the most important characteristic of a crystal. There is a constancy of the interfacial angles, though crystals may vary in size and in difference of faces according to different circumstances under which they are formed. When fractured a crystal breaks into pieces which have their plane surfaces meeting in sharp edges.

All solids are regarded as crystalline, but certain rigid solid substances such as glass and colophony do not possess all the properties of crystals and are regarded as supercooled liquids. The latter have a very high viscosity. Their molecules are very complex and not usually arranged in the way necessary to give crystalline form. When fractured they break as easily in one direction as in another.

While crystals have been described in simple and obvious terms such as needle-shaped or as prisms, plates and so forth, terms like these are of no help in the classification based on the disposition of the crystallographic axes.

It has been found by X-ray analysis of crystals that the constituent particles are arranged at the points of lattice structures of different types. Ions occupy the corners of the lattice in true salts; in sodium-chloride crystals sodium and chlorine ions are arranged in a cubic lattice. In the diamond a carbon atom has 4 other carbon atoms arranged around it in a tetrahedral lattice. Instead of ions or atoms the particles occupying the corners of the lattice may be molecules, as in the case of non-ionized organic compounds. The structure of many compounds has been determined by X-ray study, as for instance that of benzylpenicillin (penicillin G). Silk, cellulose and wool have minute elongated crystals distributed in parallel fashion in the length of the fibres.

Many substances of similar chemical composition form crystals which are similar in shape (isomorphous); for example, magnesium sulphate and zinc sulphate, and the alums. Not uncommonly, however, substances have similar crystalline form without any similarity in the chemical constitution.

The water of crystallization in certain crystals, for example copper sulphate pentahydrate, forms part of the structure of the crystals. In this particular compound, 4 of the molecules of water are attached to the copper (cation) and one is more firmly attached to the sulphate (anion). In alum there are 24 molecules of water combined with the aluminium-sulphate molecule. There are of course crystalline salts which contain no water of crystallization.

The process of crystallization most times involves crystallization from a solvent, the crystals separating commonly during cooling; the rate of the crystallization and the size of the crystals depend on a number of factors. Substances produced by precipitation are usually microcrystalline. Here again there are several factors which determine the character of the precipitate. Novel processes have been devised for the manufacture of micro-crystalline drugs. By taking advantage of different solubilities crystalline substances may be obtained free of associated impurities. By repeated re-crystallization the material may eventually satisfy physical and chemical tests for purity.

The water of crystallization may be driven off by heat or spray drying to yield exsiccated forms of a drug; such exsiccated compounds are not necessarily anhydrous.

Doctors these days do not see many drugs in the form of crystals, because most drugs are put up in tablets or capsules or in solution for injection. The pharmaceutical chemist must have an understanding of the physico-chemical properties of solids and liquids. A recently revised and modernized text-book is now available to those interested in the various aspects of modern pharmaceutics.[1]

1. Davis, H. (1954): *Bentley's Textbook of Pharmaceutics*, 6th ed. London: Baillière, Tindall and Cox.