VIEWS ON BLOOD REGENERATION

By Professor C. D. de Langen, Professor of Medicine and Dean of the Faculty of Medicine, University of Batavia.

Immediately before his departure for Java, after a short visit to South Africa in the early part of this year, Professor C. D. de Langen, on the invitation of Professor W. H. Craib, kindly delivered a lecture to the senior medical students of this University on his studies on blood.

In accordance with the organisation adopted by the University of Batavia, Prof. de Langen spends alternative years in Holland and Java; he is in the fortunate position of being able constantly to compare diseases in the Dutch East Indies and Europe. Having the enormous number of three hundred and fifty (350) beds under his personal control, a large percentage of which are cases of blood diseases, he has utilised this opportunity to make valuable comparative anthropological contributions to our knowledge of normal and abnormal blood conditions.

The following notes on his lecture should prove interesting to those who were not fortunate enough to hear him:

"The racial incidence of anaemia in the population of Batavia is most instructive. Haemolytic jaundice, pernicious anaemia, blackwater fever, and the typical anaemia of sprue are exceedingly rare among the native population; and yet they occur as commonly as elsewhere among the local Europeans. In these diseases the cause of anaemia is increased haemolysis. Similarly sprue, a tropical disease, considered kindred to pernicious anaemia, occurs only amongst Europeans. Hookworm and chronic malaria are seldom seen in Europeans, Japanese and Chinese, though they are common amongst the Javan natives. The anaemia of chronic malaria and of hookworm diseases is due to haemopoietic failure of the bone marrow. Such paralysis of the bone marrow, or aplastic anaemia, is practically confined to the native population.

A European with hookworm disease does not exhibit anaemia at all unless he has had a very heavy infection over a long period of time; but a native very quickly shows anaemia even with a mild infection. After an attack of malaria, a native displays severe anaemia for weeks or months. A European quickly recovers his normal blood picture after a severe loss of blood from any cause such as injury or operation, but a Batavian native does not.

From these facts it is evident that the aplastic type of anaemia is more common amongst the East Indian native population whereas the haemolytic type occurs oftenest in the European.

The importance of such studies for us in South Africa lies in the fact that investigation of the Hospital records throughout the Union and the Congo, has shown the same conditions as obtain in the Dutch East Indies. Pernicious anaemia and blackwater fever are very rare among the Bantu natives in this country; only one case with the diagnosis of pernicious anaemia rewarded the searches through these records. Further, anaemia in Bantu natives persists longer and is more severe than in Europeans.

Now pernicious anaemia is stated by some authorities to be a dietary deficiency disease. But primitive races generally suffer more from deficiencies in diet than Europeans. Remediing the dietary deficiency by liver administration is efficacious in pernicious anaemia and in the anaemia of sprue amongst Europeans, but a liver diet is valueless in the aplastic anaemias of the tropical Javan natives.

In order to understand these differences in bodily response in diseases of the red cells, it is necessary to understand destruction and regeneration as it occurs in the normal human
body. Each red blood corpuscle has a certain lifetime, after which it disappears from the circulation and is replaced by a new one. Destruction and regeneration are in a state of equilibrium in normal individuals, so that the number of erythrocytes remains constant.

The life span of a red blood cell is said to be from 10 to 150 days, according to different authorities on the subject. Professor de Langer spent last year in determining, as exactly as possible, the life time of red blood cells:— Human blood is constantly being haemolysed; the haemoglobin is transformed into haematin, with the loss of globulin in the process, and thence to bilirubin. The latter is excreted by the liver, and leaves the body through the faeces and urine as urobilin. This may be expressed graphically as follows:—

Erythrocytes — haemoglobin — haematin — bilirubin — urobilin. By estimating the amount of urobilin in excretory products one can calculate the amount of bilirubin formed in twenty-four hours, and hence the quantity of red cells necessarily haemolysed to produce that amount. Not all the haemoglobin freed in the process of red cell destruction is excreted; the iron radicle is retained in the body to be used as building material for the new cells; this retained haemoglobin is said to represent not more than 5 per cent. of the total haemoglobin released by red corpuscular destruction.

Investigation by this method (i.e. the measurement of excreted urobilin) has shown that the life of the red cell in Holland is 155 days. Therefore, the quantity of blood destroyed every day is 30 cubic centimetres. Among the natives of India it has been calculated at 212 days; and among the natives of Java at 205 days. The daily destruction of blood in a Javan native is less than in a European by about a half. These are average figures but they show that the life-time of the red cell is longer in the native peoples than in Europeans. If the method of estimation is fallible, the errors obviously apply to both groups and the comparison still holds. Urobilin is excreted by the European in a proportion 50 per cent. greater than the Javan native.

It appears that diet exercises a great influence on the rate of blood destruction and regeneration, and that variations in the term of life of the erythrocyte in different persons may be explained, at least in part, by differences in their diet. In the case of the natives of Java, their diet is frugal and has the following characteristics: (1) a predominance of carbohydrate; (2) less protein than in that of Europeans, chiefly of vegetable origin; (3) the fats and lipoids are of subordinate value and are also derived mainly from the vegetable kingdom. European "vegetarians" living on fish, cocoanut oil and vegetables show a urobilin excretion similar to that of the Javan native. Experimentally, a person on a carbohydrate diet for a sufficient length of time increases the life of the red cell, while a mixed diet of rich foods diminishes it. One is forced to the conclusion that food content controls the life of the red cell.

The regulation of the blood state is vividly illustrated by experiments on rabbits. A rabbit bled daily for three days, to such an extent that on the third day the red cell count is only one-third of the normal, requires many weeks to return to the normal, if fed merely on grass and turnips. But if oats are added to the diet then three weeks only are sufficient to regain the 100 per cent. mark; and if oats alone form the diet, the time drops to two weeks. On an oats diet, the animal excretes an enormous amount of urobilin. The haemolysing action on the red cells of the lecithin content in the oats diet is so marked that even a pink serum might develop; but the regeneration of the red cells is equally active and the total count remains constant.

The diet of man influences the life time of the erythrocyte in the same way and this explains the rate of haemolysis and regeneration.

The covering membrane of the red cell is like a chemical mosaic. It contains lecithin and cholesterol. These substances are antagonistic from the point of view of both physiochemistry and bio-chemistry. Lecithin causes a prompt and complete haemolysis; this action is inhibited ordinarily by the presence of cholesterol which has the reverse influence. The presence of both substances produces a state of equilibrium. When red cells are washed in Ringer's solution a large part of the lecithin is removed and the resistance of the cells to haemolysis is thereby increased. But if lecithin is added to a suspension of the cells, the resistance is decreased. The addition of oats (rich in lecithin) to the diet of the rabbit referred to above, greatly increases the haemolysis of the animal's red cells.

Both of these important lipoids occur in a normal full diet, and both are deficient in a diet which is poor in animal fats.
With regard to the mechanism underlying the regeneration of red cells, it appears that the death of one cell provides the stimulus for the formation of another. Even if haemolysis is increased the total number of red cells remain constant. Though the diet may be changed, the number of erythrocytes persists at the normal level. When the life time of the individual cell is prolonged (by diet) the regeneration of cells is slowed down. Haemolysis can be increased (by the same influence) but regeneration follows rapidly; when it is diminished regeneration is slow. The European on rich mixed diet has a rapid haemolysis accompanied by rapid regeneration; the native on a poverty-stricken and limited diet has a slow rate of haemolysis correlated with a slow process of regeneration.

Is haemolysis primary and regeneration secondary? To understand the relationship between these processes, we must revert to our rabbits bled on successive days until on the third day the red cell count is one third of the normal. If 5 c.c. of haemolysed blood is injected into such an animal it recovers in ten to twelve days (i.e. even less time than it takes to recover on a full oats diet). If the dose of haemolysed blood is too large, regeneration is pushed to such a point as to bring about paralysis of the bone marrow. Injections of haemoglobin in the same way produce regeneration in twelve days; of bilirubin, sixteen to twenty days; of iron and copper, eighteen days; of haemolysed liver cells, fifteen days; of spleen, fourteen days; and of bone marrow a very short time indeed. The most potent regenerating factor is haemolysed blood; this is not surprising when the dead or haemolysed red cell is always producing material which stimulates the bone marrow to regenerate or produce new red cells.

It is through such experiments as these that we understand why blood transfusion is most valuable in aplastic anaemia, but has only a temporary effect in pernicious anaemia and has never saved the life of a person suffering from blackwater fever. The beneficial effect in an aplastic anaemia is due to the activating influence of the haemolysed erythrocytes on the bone marrow. A small amount of haemolysed blood administered intramuscularly gives as good (if not better) results, than transfusion. Good food, that is a rich mixed diet, and the administration of iron are helpful by stimulating the same sort of haemolysing and marrow-stimulating effects.

The incidence of aplastic anaemia amongst Javan natives as compared with Europeans is therefore due to the difference in red cell metabolism depending upon the difference in diet. Pernicious anaemia occurs chiefly amongst people whose diet is rich and mixed. Haemolytic anaemia is the sign-post of a wealthy life; aplastic anaemia that of poverty.

Those interested in following the subject further and in appreciating how many and how varied are the investigations upon which Professor de Langen’s opinions are based are advised to read his splendid article “Studies on Blood Diseases and Blood Regeneration in Java,” which appeared in the Proceedings of the Royal Society of Medicine, Vol. XXVI, No. 6, April 1933.

PSYCHOLOGY AND MEDICINE

Psychology . . . demands on the part of the physician, something more than acquaintance with Medicine as taught in the schools. Unless there is a pretty wide knowledge of human types, of life situations, of trends of thought, and of human nature in all its aspects, psychological appreciation is impossible. The wider our own experience, the greater our knowledge of the human heart and mind as dissected in art and literature; and the fuller our acquaintance with the views held of religious, philosophical and ethical problems, the more successful our efforts. Perhaps that is the meaning of the maxim that at fifty one is either a fool or a physician. F. G. Crookshank, “The Psychological Interest in General Practice.”