Original Articles

THE ANÆMIA OF PREGNANCY*

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AMONGST recent papers on the ætiology of this obscure disease, one may mention those of McSwiney (1927), of Balfour (1927, 1929), the work of Wills and Mehta (1930) and of Wills (1931)—largely relating to dietaries, and of Maitra (1931).

This anæmia occurs in Bengal as a distinct disease associated with pregnancy. The usual causes of tropical anæmia are ancylostomiasis and other helminthic infections, malaria, leishmaniasis, dysentery, tuberculosis, syphilis and sprue, all responsible, more or less, for tropical anæmia. The extent to which one or a multiplicity of these diseases are involved in the ætiology of pregnancy anæmia is an important question which will be discussed in detail.

There is certainly a large group of cases where the above-mentioned factors are wanting. The condition of pregnancy seems to be essential and not a mere accident in this malady.

The symptom-complex, the blood picture, the course of the disease and the dramatic end of these cases, the morbid anatomy and histopathology are invariably the same. What I saw of this ailment in 1920 when I was first attached to the Eden Hospital was also true in 1931.

It is a disease in entity as distinct as pernicious anæmia of the Combe-Addisonian type. These will perhaps cease to be distinct disease groups when an ætiological factor or factors common to both can be found out.

Clinical features.—A fully developed picture of anæmia complicating pregnancy makes as indelible an impression on the mind of an observer as does that of a pernicious anæmia. The face is pale and the conjunctivæ white; the whole surface of the body has a flabby œdematous appearance. The emaciation is much less than one would expect from the degree of the anæmia. Puffiness of the face and œdema of the feet and ankles, in fact a generalised œdema is seen in a fair number of cases. Some of them are remarkably sthenic and can easily carry on ordinary household duties, but much strain or any attempt to climb up a staircase will cause palpitation and breathlessness. Early digestive disturbances are commonly noticed. The tongue is glossy and flabby, soreness of the tongue is noticed in some patients but is not constant. Diarrhœa is a common complaint. The pulse tension is considerable but compressible. Blood pressure is low. Most of the cases suffer from a slight rise of temperature.

The picture drawn above is typical of 'pregnancy anæmia' in Bengal. It occurs in all communities, both in villages and towns, amongst Hindus, Mohammedans and Christians. The urban districts suffer more than rural areas. The so-called middle class women and poorer classes of Bengal suffer more than the better and richer classes of people. Anglo-Indians and Jews suffer less in proportion as well as in severity than do other communities. Europeans are practically unaffected.

Number of cases and the condition of patients on admission

The present series consists of 203 cases ; all of them were admitted into the Eden Hospital as indoor patients during the period August 1928 to July 1930. Most of them were admitted in the last trimester at or near full term. Opportunities were available to study the cases in detail, but most of them left the hospital at their own risk as soon as a slight improvement was noticed, as their presence at home was urgently required. A few remained longer, for a cure, but the hospital accommodation was insufficient to allow them to remain in hospital for a longer period. This constituted one of the principal difficulties in a 'follow-up' of the cases and in ascertaining the end-results of treatment. This series also included a few cases complicated with secondary infections, such as malaria (2 cases), ancylostomiasis (2 cases), amœbic dysentery (1 case), syphilis (15 cases). It will be seen that the anæmia of the patient was hardly improved during pregnancy at the third trimester even after amelioration of the secondary infections.

The hæmatological findings in anæmia of pregnancy

The changes in the blood are an important feature of the disease and are essential for making an accurate diagnosis.

The grade of anæmia met with in this series of cases is tabulated conventionally in 3 groups :—

(*i*) *Group I* includes cases where the red cell count was 1,000,000 per c.mm. or less—36 cases recorded.

(*ii*) *Group II* includes cases where the red cell count was between 1,000,000 and 2,000,000 per c.mm.; 114 cases recorded.

(*iii*) *Group III* includes cases where the red cell count was between 2,000,000 and 3,000,000 per c.mm.—53 cases recorded.

The mean average red cell count of the above three groups was 1,530,000 per c.mm., the average colour-index was 1.1, and the average leucocyte count was 7,485 per c.mm. (excluding

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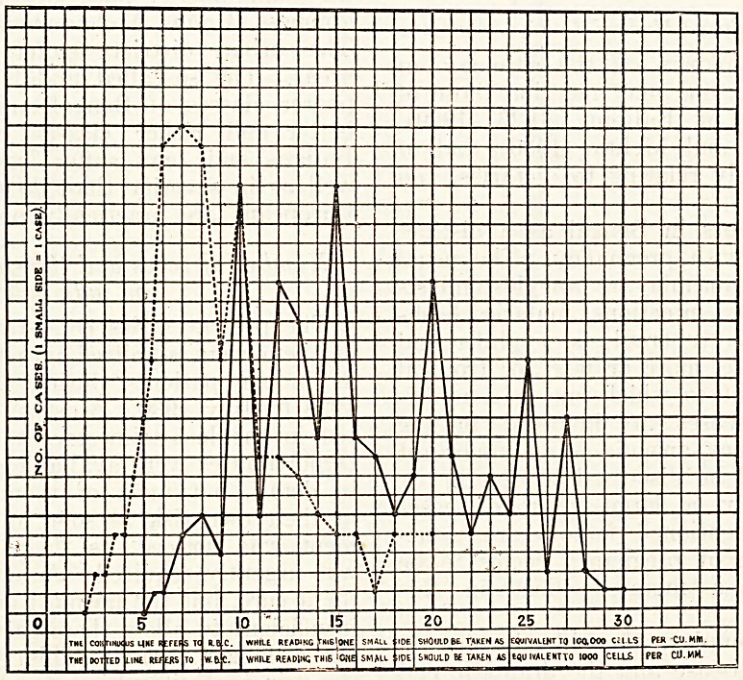
cases with high leucocytosis). Graph I represents red cells and leucocyte counts. This includes all cases and even those with high leucocytosis; an average increase of leucocyte count is represented.

the corpuscles seems generally greater than normal.

Macrocytosis is not easily detected. In fact, macrocytes have been missed except in a few cases which were of a definitely megalocytic

Graph I



Graph I represents red cells and leucocyte counts.

The average blood conditions of pregnant Bengali women of the hospital class was studied in 55 cases to find its relative significance in connection with anæmia in pregnancy.

The average red cell count of this class of women was 3,000,000 per c.mm. and the average percentage of hæmoglobin 55 per cent. The colour-index was 0.9. The average white cell count was 7,000 per c.mm. and the average reticulocyte count was 1 per cent.

Blood picture and reticulocyte count in the anæmia of pregnancy

The morphological changes in the blood picture have been observed in cases of profound anæmia, and also contrasted with those of cases approximating to the normal average of the hospital class of patients. The outstanding feature is the decrease in the red cell count which is sometimes so low as to give a peculiar watery appearance of the blood which is very familiar to us. Anisocytosis, poikilocytosis, polychromatophilia were observed in 74.3 per cent. of cases. Punctate basophilia was observed in 20 per cent. of cases. Normoblasts or pronormoblasts were seen in 25 per cent. of cases.

True megaloblasts were seen in 0.4 per cent. of cases. The mean variation in the size of

character. In doubtful cases the method suggested by Lowy was adopted. All these features show an active regeneration of the marrow. Evidences of corpuscular regeneration are thus found due to hyperplastic changes in the bone-barrow. Anomalies of cell reproduction are also met with.

Only a few cases responded by an increase in the reticulocyte count after liver diet. The total average increase in those cases responding to liver treatment was 5 per cent. only.

The response to liver diet is thus not similar to that in the 'pernicious type of anæmia'.

Red cells, hæmoglobin and colour-index

The number of red corpuscles and the amount of hæmoglobin do not decrease equally. The average colour-index as stated before was 1.1. A high colour-index supports the macrocytic nature of anæmia in this ailment. It is to be seen, however, that high colour-indices are not present in every case in this series. The hæmoglobin value was taken by Sahli's method or modified Sahli (Hellige).

White cell count.—Unlike the leucopænia in 'pernicious anæmia' there is leucocytosis in our series of cases. The average white cell count was 7,430 per c.mm. There was also an average relative increase in the percentage of

neutrophiles. Fifty-six per cent. of cases showed an average increase of neutrophiles to 70 per cent. in the differential counts.

Leucocytosis as a physiological condition is seen in pregnancy. In our control series, the average leucocyte count was 7,000 per c.mm.

Platelets. The general appearance of the slide shows a decrease in the number of platelets. Platelets are not ennumerated and are not shown in the blood count.

Wassermann reaction. This was positive in only 8.5 per cent. of this series.

Bacteriology of urine and fæces in cases of anæmia of pregnancy

In the examination of the urine, 25 per cent. of our cases in this series showed albumen. Colon bacteria were recovered from the urine in 50 per cent. of post-natal cases. Antenatal cases were practically free. Five per cent. of the positive cases were found hæmolytic. Atypical strains of this group were also encountered in a few cases. Fæcal streptococci (enterococci) were often seen.

The routine of urine culture is to centrifuge a catheter sample for about ten minutes till all sediment deposits at the bottom. The supernatant fluid is thrown off and a drop of the deposit is plated on (*a*) MacConkey's medium, (*b*) a loopful is plated on bromcresol purple-lactose agar, (*c*) a small amount is inoculated on saline agar surfaced with a thick layer of 5 per cent. defibrinated human blood.

A wet preparation gives information regarding (*i*) motility of the bacteria, (*ii*) the presence of pus cells, (*iii*) casts or crystals, (*iv*) or any other abnormality.

Three smears are prepared, one on a cover slip mounted in 1:5 methylene blue, blotted, then is instilled a drop of 0.5 per cent. acetic acid, to study the morphological characters in detail, the second smear is treated by Gram's method, and the third stained for acid-fast bacilli.

It is a wrong idea to think that colon bacteria cannot be recovered from an alkaline urine; pus cells are absent in a case of simple bacilluria. Those strains which morphologically appear like pneumococci are really enterococci. It is difficult to suppose that this disease is associated with any particular variety of these bacteria.

The efforts to study the fæcal flora were directed to the discovery of specific pathogenic organism. Technical details were followed after Davidson.

Except in some isolated individuals, the strains of bacteria recovered from the intestinal flora do not differ from those found in healthy persons.

The fæcal flora of ten healthy women, on an average Bengali diet, were examined to compare the findings with those in anæmia of pregnancy.

It was found that the total number of bacteria was greater in anæmia cases than in normal women. Further light could not be gained and I found it hopeless to classify them on a really informative basis.

Atypical colon bacilli were encountered in a few cases. A group of non-lactose fermenters (*B. carolinus, B. asiaticus* and others) and late-lactose-fermenters were met with. None of these strains were found to be hæmolytic.

Streptococci were classified on biological methods into hæmolytic and non-hæmolytic, and further differentiated into broader groups by fermentative tests. A number of anærobic streptococci were also met with.

Selection of culture media for the urine was the same as that in our routine examination of fæces. Bromcresol purple lactose agar as recommended by Moench Kahn and Torrey was found suitable, particularly for enterococci, as it is sensitive to colour change. They appear as small colonies, fairly thick with a light yellow periphery and a dark centre. They are ovoid in shape, of short chains, can resist temperature to 60°C. for 20 to 30 minutes. They grow in MacConkey's media (bile salt media) and give a general turbidity in broth with a very little deposit. They ferment lactose, salicin and mannite.

The other streptococci, including enterococci encountered in the fæcal flora, were all inert to blood.

Long-chained streptococci of the *salivarius* group were met with. They do not grow in bile salt media.

Ten cases were examined for *B. welchii* and two of them were found positive. The method adopted for this purpose was William and Blair's modification by Davidson. Opportunities were not available to examine systematically the gastro-intestinal flora in different trimesters, and also to follow the changes after pregnancy. From the analysis of the results no causal organism with approximately the same frequency of incidence in each case could be found.

In our everyday routine work we meet with atypical colon bacteria like *B. carolinus* and others, or a few hæmolytic strains of *B. coli* or *Sr. salivarius*. None of them appear invariably in our series of cases. All that can be said is that the fæcal flora is different quantitatively from that of the normal healthy individuals.

The same thing may happen in pregnancy with the uterus pressing more or less on the surrounding tissues, particularly the large intestine.

It has been demonstrated that these patients do not suffer from achlorhydria (Lucy Wills) and so any infection from the upper alimentary tract is apparently not possible; the acid gastric contents kill any bacteria swallowed.

The possibility of extension from the colon to the higher level of the small intestine is much

more feasible. Lieut.-Col. Acton also believes in intestinal sepsis as a factor.

The bacteria normally present in the intestine under such conditions may behave pathologically and result in entero-colitis, as frequently manifested in these cases. They behave as extrinsic factors only.

It is a well established bacteriological belief that each disease is caused by one species of organism, but our examination of the fæcal flora has failed to find any such bacterium.

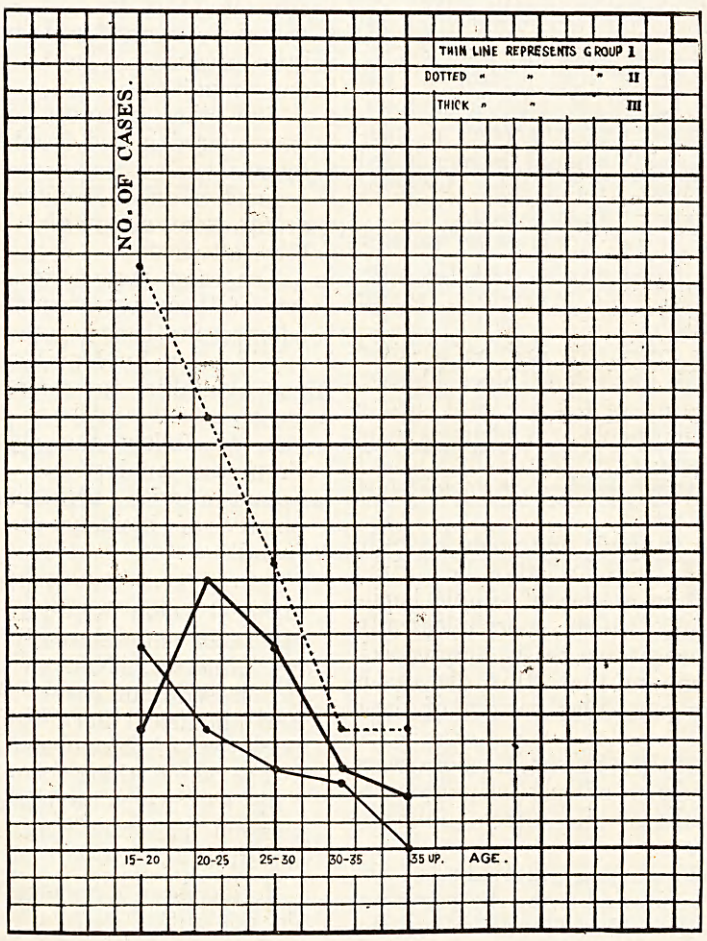
however, observe strict purdah and are reluctant to seek admission to hospitals, and so a smaller percentage of this community is shown in this series. An average percentage of the different communities suffering from different grades of anæmia is shown below :—

Hindus	.. .. ..	57.9 per cent.
Mohammedans	.. ..	10.24 „
Indian Christians	.. ..	27.5 „
Anglo-Indians	.. ..	3.13 „
Jews	.. .. ..	1.23 „

Incidence of the disease in different communities

	Europeans	Anglo-Indians	Indian Christians	Hindus	Moham-medans	Jews	Total
Number of cases admitted (August 1928 to July 1930).	73	1,022	244	1,304	110	68	2,821
Number of anæmia cases during this period.	..	8	55	116	21	3	203
Incidence, proportion ..	..	127.8	4.4	11.4	5.2	22.6	13.8

Graph III



Graph III represents age incidence.

Communities.—All communities are admitted to the Eden Hospital, but Mohammedans

Graph II represents the number of cases, in columns, and the correlations of the different

communities suffering from the different grades of anæmia (Groups I, II and III).

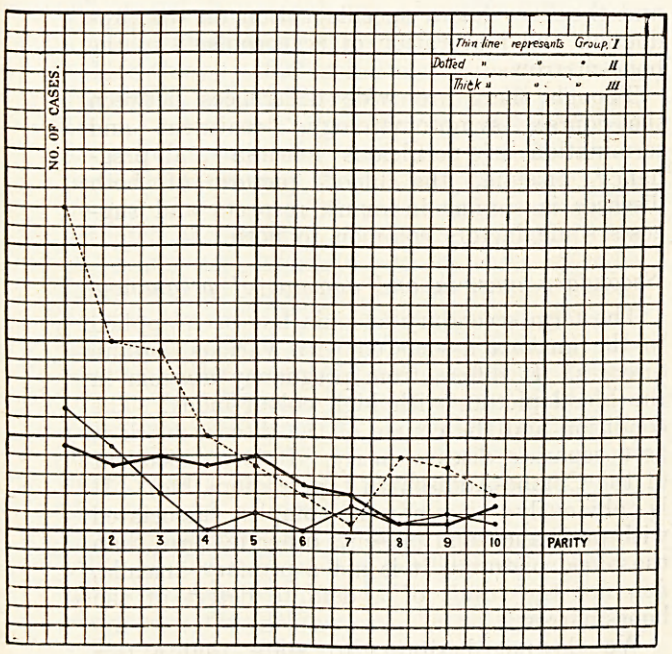
The number of Hindus admitted to the Eden Hospital is highest, the percentage of Hindus suffering from anæmia is greater than the other communities and more so in Group I (*i.e.*, the severest grade of anæmia). The Anglo-Indians and the Jews suffer less in proportion as well as in severity, as they seek early antenatal care.

The Indian Christians too, attend antenatal clinics at the out-patient department more than do the Hindus and the Mohammedans. Their percentage is highest in Group III, *i.e.*, the low grade of anæmia.

Unlike Hindus and Mohammedans, the other communities possibly do not wait for severer symptoms but seek admission whenever any complaints appear during pregnancy.

It should be mentioned that the hospital admitted more cases with anæmia of pregnancy during this period in order to study this ailment particularly, and so the incidence of the disease should not be accepted as strictly normal. The incidence is highest amongst the Indian Christians, as this group of 'hospital class' of this community in Calcutta seek early antenatal care and hospital admission.

Graph IV



Graph IV represents parity incidence.

Age.—(Graph III). The highest frequency of anæmia of pregnancy is between the ages of 15 and 20 years with a steady decline after 25 years. There is a slight deviation in Group III where the highest incidence is between the ages of 20 and 25. This is due to the inclusion of a relatively greater number of communities other than Hindus and Mohammedans, who marry at a later age.

Parity.—(Graph IV). Primiparous women are most affected; then follows a gradual decline more or less to 7th gravida and then a sudden rise at 8th and 9th gravida.

Hygienic survey and dietetic studies

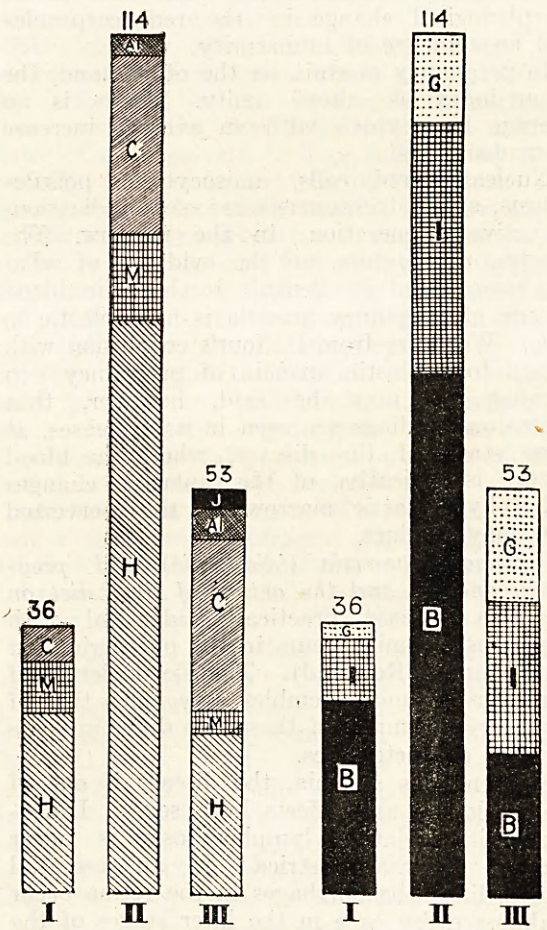
It is important to enquire into the home conditions and diets of these patients. In doing so one has to depend on the statements of the patients and their relations.

Graph V represents the hygienic survey into good, indifferent, and bad conditions and their

Graphs II and V

Graph II represents community incidence.

Graph V represents hygienic survey into good, indifferent and bad.



Graphs II and V are placed side by side to show the relationship between the hygienic condition and the degree of anæmia in pregnancy. Those with better hygienic conditions suffer from a lesser grade of anæmia.

correlation in the three grades of anæmia (Groups I, II and III). It seems reasonable to think that there is some relation between the hygienic condition and the degree of anæmia in pregnancy. Those with better hygienic conditions suffer from a lesser grade of anæmia. There is no direct relationship, but the mode

of living and the dietary certainly influence the disease. This is a presumption and invites investigation into the dietary and hygienic condition of these patients.

Studies in pernicious anæmia of pregnancy in Bombay by Wills and Mehta (1930) suggest that defective nutrition is a contributory cause of 'pregnancy anæmia'.

Liver and spleen.—10.63 per cent. of cases showed an enlarged liver and 8.8 per cent. of cases showed splenic enlargement.

Pyorrhœa.—11.8 per cent. of cases.

Aplastic anæmia and pregnancy anæmia.

In aplastic anæmia, the colour-index is near unity. The progressive leucopænia and the absence of regenerative activities, even for a short period, are prominent features. The granulocytes are diminished, and there is no morphological change in the red corpuscles and no evidence of immaturity.

In pregnancy anæmia on the other hand, the colour-index is above unity. There is an average leucocytosis with an average increase of neutrophiles.

Nucleated red cells, anisocytosis, poikilocytosis, and polychromasia are clear indications of active regeneration in the marrow. The conclusion therefore, on the evidence of what we have found in Bengal, is that the blood picture of pregnancy anæmia is not aplastic in type. We differ from Balfour's conclusion with regard to 'aplastic anæmia of pregnancy' in Bombay. It may be said, however, that anomalous findings are seen in a few cases, at some stage of the disease, where the blood picture is indicative of the aplastic changes which hyperplastic marrow of the perverted type may produce.

Pernicious anæmia (idiopathic) and pregnancy anæmia and the action of liver diet on them.—A disease practically identical with pernicious anæmia occurs in the puerperium or in pregnancy (Rowland). The blood picture of pernicious anæmia resembles very much that of pregnancy anæmia, but these two differ in some essential characteristics.

In pernicious anæmia, the disease is one of late adult life and affects both sexes. Leucopænia with relative lymphocytosis is never absent. 'Achylia gastrica' is an essential feature, linear hæmorrhages in the retina occur in almost every case in the later stages of the disease. There are characteristic periods of relapses and remissions. Patients may suffer from a spinal cord lesion.

Recently, another distinctive feature has emerged in the specific action of liver treatment on pernicious anæmia. In pregnancy anæmia none of the above syndromes are manifested. The anæmia does not invariably reappear in subsequent pregnancies. The course of the disease is different, the patient may die at any stage of the carrying period at or near full term, or gradually recover after delivery. Liver treatment has no specific action on the malady and there is no cure of this condition by liver treatment.

The effective treatment by liver diet in pernicious anæmia is shown by the rapid increase of the red cell count to 4 or 5 millions per c.mm. within a couple of months and cessation of other symptoms, but in pregnancy anæmia patients take liver diet for months together without appreciable increase in the red cell count or cessation of symptoms. The liver has nothing more than a nutritive value in the condition. Liver stimulates the activity of regenerative marrow in any anæmia. It has a limited action on anæmia during pregnancy as is evidenced by the blood counts before and after liver treatment.

It is interesting to observe that liver treatment acts better after the termination of pregnancy. It is possibly the termination of pregnancy that counts more towards the improvement of the patient than the liver diet, or the termination of pregnancy creates an opportunity for the liver to act properly on the production and maturation of erythroblasts in the bone-marrow.

The recent work of Minot and Murphy on extracts of mammalian liver (non-protein and iron free) suggests that the disordered hæmopoiesis is of the nature of a 'deficiency disease', and the liver has a specific action on the production and maturation of erythroblasts in the bone-marrow.

Though there are wide differences between the course, symptomatology, treatment and termination of pernicious anæmia and pregnancy anæmia, the blood picture of both diseases is similar in many respects and suggests some factors common to both.

Secondary anæmia and anæmia of pregnancy

The term secondary anæmia has been applied to the anæmia associated with various definite diseases. It differs from pregnancy anæmia in the blood picture with high colour-index. The condition and the course of the disease mark it as a separate disease entity. It is independent of the Combe-Addisonian type (idiopathic). It is obviously a syndrome-complex associated with pregnancy and presents other features than the blood picture. It is not a primary anæmia, *i.e.*, not the result of a definite defect of the bone-marrow.

We do not hesitate to state that a fair number of cases improve after the termination of pregnancy. The injury to the system and particularly to the blood forming organs is by no means negligible, and they take six months or over a year to get back to the normal blood state. In some cases, a speedy recovery is seen and the marrow resumes its normal function.

The symptom-complex of pregnancy anæmia disappears with the termination of pregnancy,

and the patient returns gradually to a more or less normal blood condition. This fact suggests the secondary nature of the 'syndrome-complex' known as 'anæmia of pregnancy'.

Anæmia due to tropical diseases associated with pregnancy

The anæmia due to ancylostomiasis is not very common in Bengal. Two cases only in this series showed ova of ancylostoma.

The anæmia due to malaria and kala-azar is certainly marked in a number of chronic cases. A few cases of chronic malaria may show a blood picture of pernicious anæmia type with high colour-index. The clinical features, the presence of parasites and laboratory methods can easily clear the diagnosis. Two cases suffering from malaria are included in this series.

In sprue, the diagnosis is loosely made because of its symptom-complex. The typical signs and symptoms of sprue are not often seen among the indigenous inhabitants of Bengal. This condition is more common amongst Europeans who are practically free from anæmia in pregnancy.

In the tertiary stage of syphilis the blood picture may resemble that of the pernicious type of anæmia (Cummer). A positive Wassermann reaction and general improvement following antisyphilitic treatment will clear the diagnosis. Only 8.5 per cent. of this series gave a positive reaction.

McSwiney (1927) in his paper on the anæmia of pregnancy reported that 40 per cent. of his cases gave a positive Wassermann reaction and suggested concealed syphilis as a probable cause of 'anæmia of pregnancy'. A doubtful reaction (30 per cent). cannot be accepted as positive. A moderate reaction (60 per cent.) and definitely positive cases must be taken into consideration. Some authors are of opinion that the Wassermann reaction gives an anomalous result in pregnancy (Kolmer). In a series of 100 cases of pregnant women admitted to the Bengali lying-in-ward, Lieut.-Col. Gow found that only 10 per cent. of these gave a positive reaction. It is difficult to accept syphilis as a cause of pregnancy anæmia when the majority of pregnant women escape from this condition. On the other hand, the possibility of the independent development of pregnancy anæmia in a syphilitic patient must be accepted. Though most of the patients do not suffer from secondary infections when admitted in the hospital, most of them gave a history of illnesses from such diseases as malaria, kala-azar, tuberculosis and chronic dysentery.

Morbid anatomy and histopathology of the anæmia of pregnancy

As the specific features in all our cases were much the same, they are described together. Any appearances observed in any particular one of them are noted separately. Descriptions of organs not showing any characteristic changes are omitted.

From a pathological view-point the most striking feature is the deposit of free iron in the internal organs of the body. If a thin slice of liver, spleen or kidneys be immersed in solutions of ferrocyanide of potassium and weak hydrochloric acid, it becomes gray-blue in colour. This is indicative of the presence of free iron. Marked fatty degeneration is present in the various organs. Myeloid metaplasia and areas of hæmatopoietic cells are also present in the liver and spleen.

The body is flabby rather than wasted. The nutrition of the body is maintained as compared with its extreme pallor. The internal organs appear pale.

Liver.—Slightly enlarged, appears fatty and brownish-red in appearance.

Histologically, the most striking feature is the hæmosiderin granules which are scattered like ferric dust in the liver cells themselves. They occupy the fine bile capillaries in the centre of each column of liver cells. They are specially marked around the portal tracts. It is rare for any secondary anæmia to show such an extensive pigmentation. Accumulations of erythroblastic cells and foci of myeloid hyperplasia are also met with in the capillaries as well as in the liver substance itself. In some areas the red cells are phagocytosed by the Kupffer's cells and their debris is seen within their protoplasm. Interlobular hæmorrhages and central fatty degeneration are marked. In others, diffuse fatty changes are seen in the central as well as in the portal areas.

Spleen.—It is enlarged. The cut surfaces show a dirty red appearance. The Malpighian bodies do not show any change. The presence of hæmosiderin pigment is evidenced by the Prussian blue reaction.

Histologically, myeloid metaplasia and hæmatopoietic changes are conspicuous features in our post-mortem cases. The cells of the reticulo-endothelial system are proliferated. The reticulum of the pulp is full of red corpuscles. Small groups of myelocytes and nucleated red cells are seen both inside and outside the venules. Debris of red cells is seen within the protoplasm of the large phagocytic cells, which are increased in number.

Kidneys.—They look swollen and pale. On section, the cut surfaces bulge out. The cortex looks blurred. Microscopically, the cells of the tubules have become enlarged and granular, and in some areas they contain droplets of hyaline material. Tubal epithelial cells have been shed in some areas and appear granular; epithelial casts are thus formed in some areas. A large amount of hæmosiderin pigment is seen as fine granules in the cells of the excreting tubules, but the glomeruli are more or less free from these granules.

Suprarenals.—The cortical cells appear to be vacuolated, the medulla is narrowed. Hæmosiderin pigment is seen within the capsule and just underneath it.

Thyroid gland.—A fair amount of hæmosiderin pigment is seen in the connective tissue, in the glandular structure, and also in the colloid secretion.

Bone-marrow.—General activity of all varieties of cells is a predominating feature. Non-granular mononuclear cells and granular leucocytes (myelocytes) are greatly in excess. Diffuse and scattered pigment granules are seen. The number of fat cells is greatly reduced and their place is taken by foci of different types of cellular mass. Phagocytosis of red cells is also observed. The picture is so far from being aplastic that it is rather hyperplastic in type.

These changes are illustrated in plates I and II—photomicrographs, and in the colour plate.

The following are details of illustrative cases, studied at post-mortem :—

Illustrative cases

Case 1. (Group I).—Mrs. T., aged 20, II gravida, admitted for breathlessness, œdema of the hands and feet, fever, and anæmia. All these symptoms appeared in the third trimester. Previous history of malaria, spleen enlarged. Hygienic surroundings—poor.

Laboratory findings:—

Blood count after admission.—

Red cells	700,000 per c.mm.
Leucocytes	6,500 „ „
Hæmoglobin ..	15 per cent.

Colour-index—1.09

Differential leucocyte count.—

Neutrophiles	61 per cent.
Lymphocytes	30 „ „
Monocytes	8 „ „
Eosinophiles	1 „ „

Blood films—anisocytosis, poikilocytosis and a fair number of normoblasts. Parasites—nil.
Tests for kala-azar—negative.
Urine—albumin, a trace. Culture—sterile.
Stool—no intestinal parasites or ova present.
Puerperium—patient was running a slight temperature and died suddenly on the 5th day of the puerperium.
Necropsy: 29th September, 1928.
Morbid anatomy.—There was general anasarca with bilateral hydrothorax and hydroperitoneum.
Skin—maintained the usual fat which appeared yellow.
Pleural cavities:—Each contained 2 ounces of thin clear fluid.
Lungs—œdematous.
Heart—no gross changes.
Liver—enlarged, firm in consistency, cut surface bulged out, fatty in appearance.
Spleen (2 lbs.) enlarged. Capsule thickened and wrinkled.
Bone-marrow (middle third of femur)—red.
Histopathology—same as that described already.

Case 2.—Mrs. S., Hindu female, aged 25, II gravida, admitted on 30th November, 1927, in 7th month of pregnancy with anæmia, general anasarca, and diarrhœa. These symptoms appeared in the second trimester. She had previous history of malaria. Hygienic condition—indifferent.

She was delivered of a still-born and under weight baby 3 days after admission and died on 6th December, 1927.

Blood count after admission.—

Red cells	1,200,000 per c.mm.
Leucocytes	7,825 „ „
Hæmoglobin ..	26 per cent.

Colour-index—1.08.

Differential leucocyte count.—

Neutrophiles ..	74 per cent.
Lymphocytes ..	20 „ „
Monocytes	5 „ „
Eosinophiles ..	1 „ „

Blood films—anisocytosis and poikilocytosis. A few myelocytes and a few normoblasts are present. No malarial parasites.
Tests for kala-azar—negative.
Necropsy: 7th December, 1927.
Morbid anatomy—
Skin retained subcutaneous fat.
Heart—no gross abnormality.
Pleural cavities—about 2 ounces of serous fluid present in both.
Lungs—œdematous.
Thyroid—enlarged.
Liver—slightly enlarged, fatty in appearance.
Spleen (9 ozs.)—fibrous in appearance.
Small intestine—pale, two roundworms recovered.
Gall-bladder—a gallstone of the size of a marble was recovered from it. Bile flow free.
Culture of the stone—sterile.
Smears from the splenic pulp and the liver tissue did not show any parasites.
Histological appearance is almost the same as already described.
The liver, however, shows areas of focal necrosis about the central vein showing degeneration and fatty changes. Hæmosiderosis present.
Spleen—connective tissue stroma greatly increased.

Case 3.—S. B., an Indian Christian female, 19 years of age, was admitted to the Eden Hospital on the 13th January, 1930, for anæmia, general anasarca, an unhealthy and sloughing cervix, and slight temperature. Spleen—not palpable. Urine—scanty.

Obstetric history.—She was a primipara, position of the fœtus L. O. A. Fœtal heart sounds—good. Patient had a normal delivery on 14th January, 1930, child weighed 5 pounds 13 ounces. She had only one suture for a superficial tear.

Temperature and pulse—normal for the first three days.

Patient had iron and arsenic treatment, 1 c.cm. injections every alternate day. Also liver diet. Temperature shot up to 105°F. on the 4th day after delivery. Very little pent up lochia—not very offensive. Patient died on the 24th January, 1930.

Laboratory data on admission. Urine—albumin, a trace. Sediment:—a few red corpuscles, epithelial cells, pus cells, calcium oxalate crystals and micro-organisms. Culture:—Yielded *B. coli communior* (hæmolytic).

Blood count.—

Red cells	1,300,000 per c.mm.
Leucocytes ..	9,000 „ „
Hæmoglobin ..	30 per cent.

Differential leucocyte count.—

Polymorphonuclears ..	78 per cent.
Lymphocytes	21 „ „
Monocytes	Nil.
Eosinophiles	1 „ „

Blood picture.—Anisocytosis and poikilocytosis.
Aldehyde and Chopra's tests—negative.
Blood culture—sterile for 48 hours.
Necropsy: 25th January, 1930.
Skin—lemon colour, subcutaneous fat normal.
There was general anasarca with bilateral hydrothorax, and hydroperitoneum. Spleen—firm, trabeculæ increased. The organ was congested.

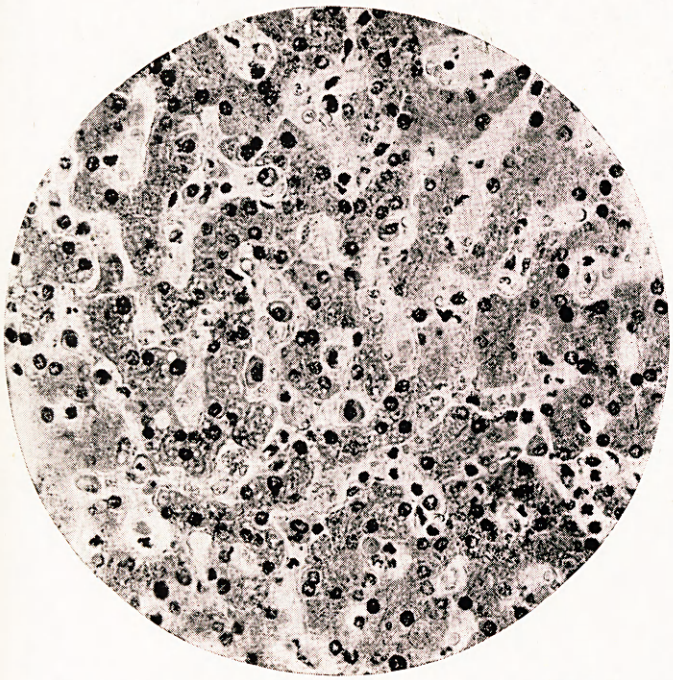


Fig. 1.—Section of liver, post-mortem Case No. 2, showing diffuse fatty changes, sinusoids are full of red blood corpuscles. Foci of myeloid hyperplasia are seen. Hæmosiderin granules are scattered like ferric dust in the liver cells.

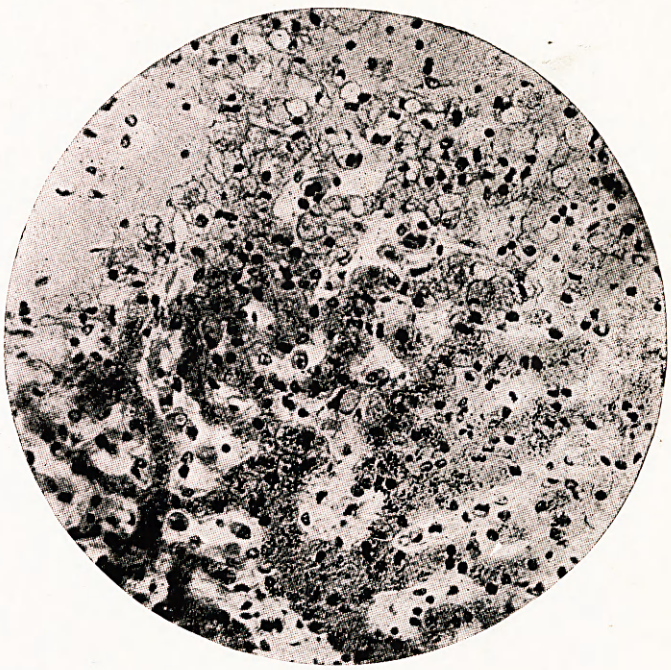


Fig. 2.—Section of liver, post-mortem Case No. 4, showing focal necrosis with cell infiltration. Fatty changes are marked particularly round the central zone. It has taken the appearance of passive congestion. Hæmosiderin granules are seen. Myeloid changes are less marked.

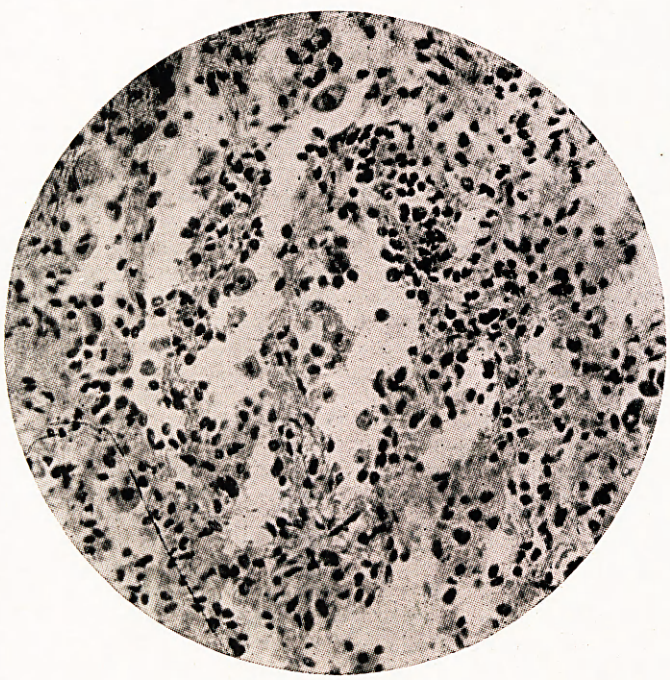


Fig. 3.—Section of spleen, post-mortem Case No. 1, showing reticulum of pulp full of red corpuscles. Small groups of myelocytes and nucleated red cells are seen both inside and outside the venules. Large phagocytic cells are also seen.

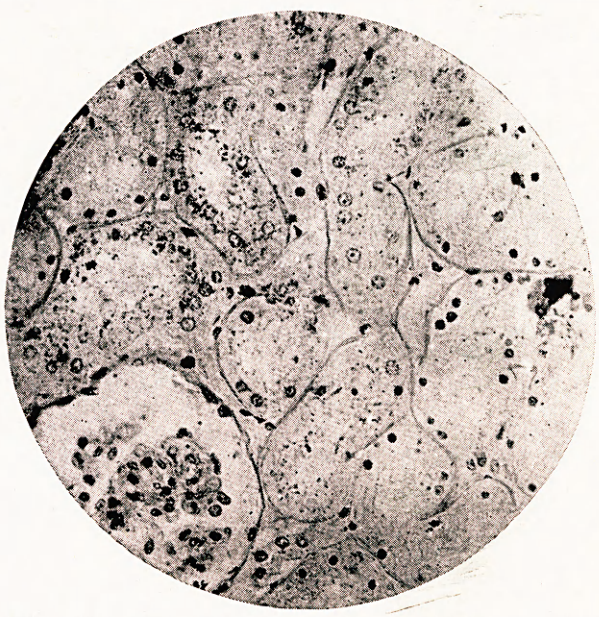


Fig. 4.—Section of kidney, post-mortem Case No. 2, showing the granular appearance of the epithelium lining the tubules. Hæmosiderin granules are seen in the cells of the excreting tubules, glomeruli are more or less free.

PLATE II

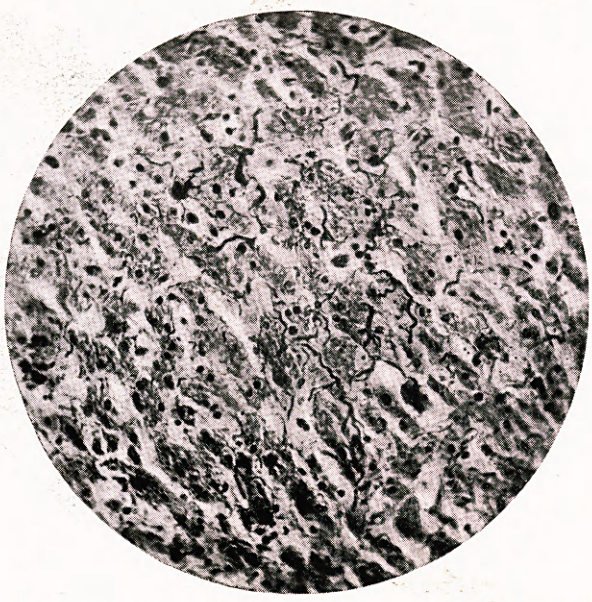


Fig. 5.—Section of liver, post-mortem Case No. 2, showing increase of fibrous tissue and reticulum.

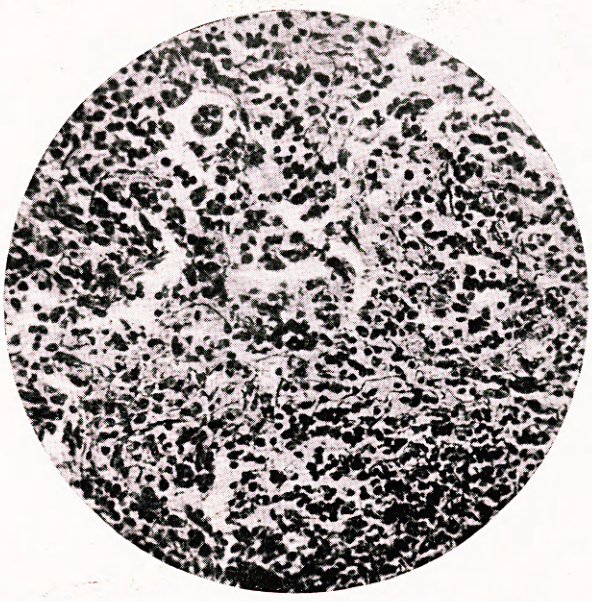


Fig. 6.—Section of spleen, post-mortem Case No. 1, showing increase of fibrous tissue and reticulum.

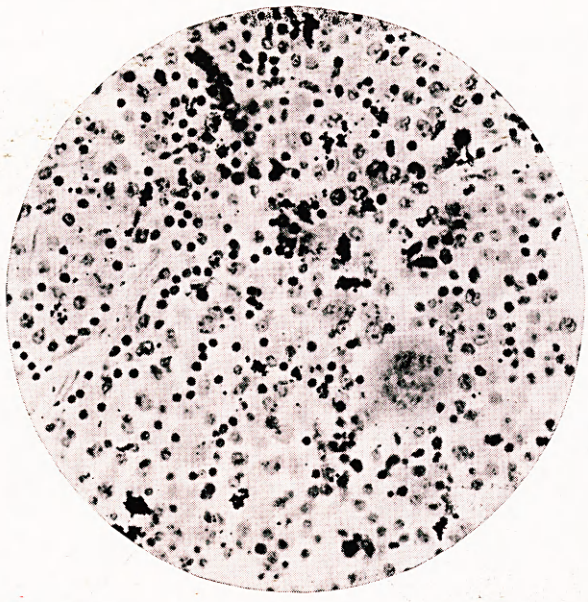


Fig. 7.—Section of bone-marrow, post-mortem Case No. 2, showing general activity of all varieties of cells. Diffuse and scattered pigment granules are seen.

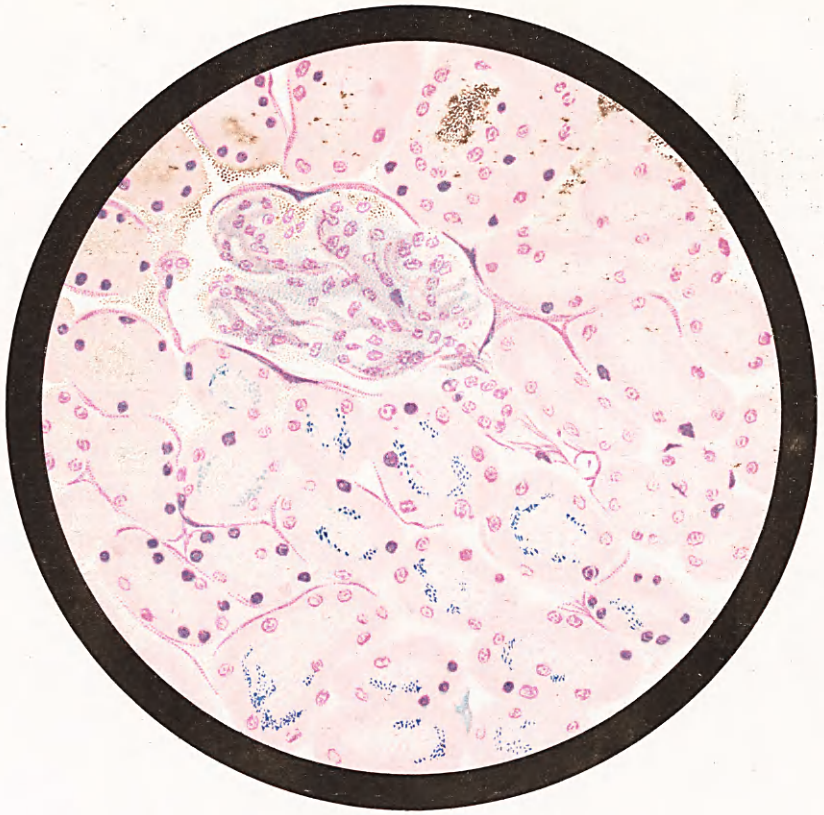


Fig. 1.—Section of liver showing hæmosiderosis, the pigment being scattered like ferric dust within the tissue.

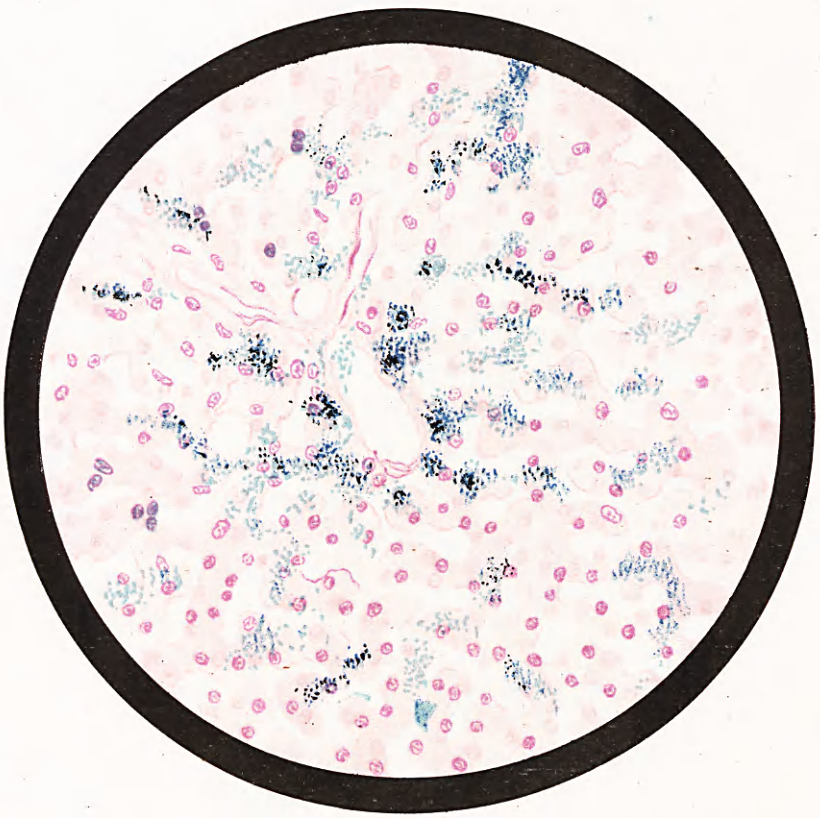


Fig. 2.—Section of kidney showing hæmosiderosis in the tubules.

Liver—enlarged, consistency—firm; pale in appearance, cut surface looks yellowish and fatty. Kidney—capsule is thickened; strips off easily, appears pale and fatty. Cortex and medulla indistinguishable.

Uterus—enlarged; site of placenta—ragged and filled with blood clots. There was a fibrinous exudate rich in leucocytes over the necrotic tissue, forming a sort of false membrane.

Culture from the scrapings yielded streptococci (non-hæmolytic) and *B. coli* (hæmolytic).

Morbid histology. Uterus—there was formation of infected thrombi in the veins. The muscle tissue was densely infiltrated with leucocytes and red corpuscles.

The infection was carried to the other organs of the body by discharge of infected emboli in the veins.

Spleen, liver, and kidney showed evidence of septic necrosis and infiltration with leucocytes. There was hæmosiderosis in all the organs. The spleen and liver showed myeloid changes.

Case 4.—J. D., Hindu female, aged 20, admitted on 17th December, 1931, for general anasarca, anæmia, and breathlessness. These symptoms appeared in the second trimester. Hygienic surroundings—poor.

Spleen—slightly enlarged; previous history of malaria. Temperature on admission 99°F. Blood pressure 120/70.

Obstetric history.—3rd-para; 7 months pregnancy; had similar condition of anæmia during last pregnancy 2 years before. Patient gave birth to 2 still-born premature babies on the 3rd night of admission. She gradually became worse and died on the 6th day of admission.

Laboratory data on admission.

Urine, albumin—a trace, no casts. Culture—sterile.

Blood count.—

Red cells ..	..	900,000 per c.mm.
Leucocytes	..	6,000 „ „
Hæmoglobin	..	20 per cent.

Differential leucocyte count.—

Neutrophiles ..	..	60 per cent.
Lymphocytes ..	..	28 „ „
Monocytes ..	..	12 „ „
Eosinophiles ..	..	Nil.

Blood picture—a few megaloblasts are present. Anisocytosis and poikilocytosis.

Wassermann reaction—negative.

Stool—semi-solid, no blood or mucus.

Culture—yielded colon bacteria.

Necropsy: 23rd December, 1931.

Morbid anatomy.—There was general anasarca with bilateral hydrothorax and hydroperitoneum. The external genitalia were greatly swollen and œdematous.

Skin—lemon coloured, subcutaneous fat retained and gave a typical bright yellow appearance of pernicious anæmia.

Pleural cavities—each contained 700 c.cm. of thin pale clear fluid.

Lungs—œdematous, no gross abnormality.

Pericardium—contained an ounce of clear fluid.

Heart—dilated; no gross abnormality.

Spleen—enlarged, firm in consistency, chocolate coloured in appearance.

Liver—enlarged, pale and appears fatty, cut surface looks passively congested.

Kidney—pale and œdematous, capsule strips off easily.

Ileum—a few actively moving roundworms were present.

Uterus—subinvoluted; uterine muscle œdematous.

Marrow—almost red in appearance, showing hyperplastic changes.

Culture from heart blood—sterile.

Morbid histology.—The histological appearance is the same as has already been described. Section of the liver, however, shows areas of focal necrosis with cell infiltration. Diffuse fatty changes are present. Fatty changes are marked particularly round the central zone. Sinusoids are full of red corpuscles.

The section shows the appearance of a passive congestion with marked fatty changes of the central zone with hyperæmia. Myeloid changes are less marked.

Hæmosiderosis is present in all the organs.

Dr. S. Mitter in his cases showed similar histological appearances in sections of the liver, and from this manifestation he concludes the disease to be of toxic origin. This seems to be rather unwarranted.

Mallory regards the necrosis of the cells as due to toxic influences usually of infectious origin and minimises the effect of changes in blood pressure. The more extreme the stasis, the more certain is the central necrosis and hæmorrhage. Others think the necrosis to depend upon stasis alone, which damages the liver tissues by asphyxiation.

Discussion

The syndrome-complex of pregnancy anæmia is rarely seen in any other condition except pregnancy in the general population of Bengal. This idea is contrary to the observation of Wills and Mehta in Bombay (1930).

It seems that the symptom-complex of pregnancy anæmia is only a manifestation of pathological changes occasioned by a variety of extrinsic factors.

The view that causation is by a bacterial toxin (probably of a hæmolytic nature) from the alimentary tract has been widely accepted since Hunter's treatise appeared. He believed that pernicious anæmia was a specific malady. Hurst admits the infective theory but advocates no single ætiological agent. Knott in 1917 found the occurrence of septic strains of hæmolytic bacteria. He found 48 per cent. of hæmolytic *B. coli* and 4 per cent. of hæmolytic streptococci in the fæcal flora. Our findings in the fæcal flora are however different. Kahn and Torrey have found an unusually large number of *Bacillus welchii* (*ærogenes capsulatus*) in the stools of patients with pernicious anæmia, and have demonstrated a soluble product which produces a similar disease in monkeys.

Many of our cases suggest a low grade of sepsis or infective condition as evidenced by a rise of temperature and leucocytosis, with a relative increase of neutrophiles.

My personal view is that no specific causal organisms exist to bring about this condition, but the quantitative increase of bacteria of the fæcal flora and their upward extension to unusual sites set up a low grade of infection and result in entero-colitis, which is frequently noticed in pregnancy anæmia. This is one of the factors which is responsible for the syndrome of pregnancy anæmia.

Recent investigations on biochemical lines suggest that some unknown hæmolysin and the lecithin of the red corpuscles, in the absence of a normal amount of cholesterol, cause hæmolysis. Red corpuscles and nervous tissue contain more lecithin than any other tissue of the body. In pregnancy anæmia, however, the nervous tissue is not affected. That anæmia of pregnancy is due to toxæmia is the theory advanced by James Young and other continental workers.

Heymann found a lipoid substance from alcoholic extracts of autolysed placenta which produced hæmolysis *in vitro*. The hæmolysin

thus elaborated is found in both the placenta and the blood, and is supposed to break down maternal blood cells. Hofbauer found a syncytial hæmolysin in the ectodermal cells of the chorion to be the cause of maternal blood destruction in early pregnancy. He concluded that the physiological anæmia was overcome in the second half of pregnancy by an antihæmolysin formed in the maternal blood. There is a tendency to give the subject of toxæmia the greater attention. Some of the cases may be of toxic origin as the majority of cases did not have any prenatal care and practically all the patients were seen for the first time in the last few weeks of pregnancy.

The theory of toxæmia is, however, difficult to maintain. It cannot explain the erythrocytopoietic as well as the leucocytopoietic activities of the bone-marrow and also the tendency to low blood pressure encountered in these cases. In this particular paper we are not concerned in the investigation of the physiological anæmia of pregnancy. We have no hesitation in thinking that some factors remain undisclosed, which are responsible for the fundamental nature of the pathological anæmia which is seen not only in this country but in other parts of the world.

Most of our cases are hydræmic in type and show increase in the water content of the plasma. Little work however has been done by us on this line. Hæmosiderosis is demonstrated in the different tissues where external blood destruction takes place. The blood destruction is caused by increased activity of the cells of the reticulo-endothelial system as manifested by erythrophagocytosis in hepatic as well as in splenic sections.

Peabody and Broun draw attention to the activity of phagocytosis of erythrocytes by cells of the reticulo-endothelial system, especially in the bone-marrow.

The hæmolysis might be due to the production of abnormal red corpuscles from a perverted erythrocytopoietic depot, and the factors which influence and result in such a condition are enumerated below.

(*a*) The analysis of the red cell count of our series of otherwise healthy women is about 3,000,000 per c.mm. This is certainly not normal, and is possibly due to the deficient intake of the proper type of material that goes towards forming blood. The average diet of the Bengali is greatly deficient in proteins and fats.

(*b*) During the first trimester in pregnancy there is insufficient intake of the proper type of food due to gastric disturbance causing nausea and vomiting, particularly marked in primiparæ.

Under normal conditions these symptoms gradually disappear and the appetite improves. In pregnancy anæmia, the appetite does not return and the patient suffers from entero-colitis, which further interferes with nutrition. She gradually becomes anæmic. Added to this, the daily routine of the house is a great strain on her system and the environmental conditions are not refreshing in the majority of cases. Most of them neglect antenatal care and develop a typical picture of pregnancy anæmia at the end of the third trimester, when they seek admission to the hospital only for delivery.

(*c*) Most of the patients suffer from some form of anæmia-producing tropical diseases at some period in their lives. This factor is very important. The effects of these diseases on the blood-forming organs are by no means negligible. The damage to the hæmatopoietic system is hardly tackled in most cases because the treatment is given up as soon as the patient finds a slight amelioration of her symptoms.

The above factors disturb the balance of the blood-forming organs and create a field of perverted erythrocytopoiesis in pregnancy, so that abnormal red corpuscles might be easily and unduly destroyed in the spleen or liver.

The syndrome-complex is thus a manifestation of a pathological entity. The variability of the symptoms is due to various factors, one or other or a group of those mentioned above may bring about this pathological entity.

Treatment

From the foregoing discussion I consider the syndrome-complex of pregnancy anæmia can be averted by prophylaxis and early antenatal care; a general improvement in health by proper dieting; and improvement in the general social and economic conditions by a better mode of living.

The value of birth control should be demonstrated to those who suffer from anæmia.

In these cases abstinence should be preferred to contraceptive means. The husband should be made conscious of the serious consequence of conception with pre-existing anæmia. All efforts should be concentrated on the first half of pregnancy when proper antenatal care is all important. It is the total nutrition that matters much in our cases in Bengal. It is a wrong idea to think that rich people do not suffer from pregnancy anæmia.

Some general remarks on the treatment of cases of pregnancy anæmia by the Obstetric Physician of the Eden Hospital may here be quoted :—

During the first trimester, the husband should be advised to humour his wife in her choice of diet, but at the same time should give her judiciously a diet with plenty of vitamines, and maintain a proper nutrition.

Any foci of sepsis should be removed. If in spite of all treatment severe anæmia supervenes in the first three months of pregnancy, particularly if there is a previous history of pregnancy anæmia, interruption of the pregnancy should be definitely advised.

We rarely meet with a case of severe anæmia at this stage of pregnancy in the hospital, but in private I have seen these cases successfully treated by emptying the uterus.

The question of specific treatment does not arise as most of them do not suffer from a specific disease. Antiluetic treatment would naturally be accorded to cases showing a positive Wassermann reaction.

At the beginning of the second trimester, particular care should be taken to improve digestion and aid proper assimilation of food.

A balanced diet should be recommended in an easily digestible form. Milk preparations in all forms made palatable and easily digestible should be allowed.

Fresh fruits, honey, gur, vegetables and liver extracts or any preparation of liver which happens to please the patient, are the routine treatment of the Eden Hospital. Thyroid and calcium may help.

My own idea is that liver or vitamine treatment, alkalies and bitters, will have a better result in the first half of pregnancy. They can have very little action in the third trimester, owing to the inhibitory effect of sepsis on liver treatment. Pre-existing anæmia should be primarily treated.

We welcome the recent publication on the treatment of 'pernicious anæmia' of pregnancy with Marmite by Lucy Wills. It was used to prevent disease amongst the troops in Mesopotamia, and Lieut.-Col. Leicester used to prescribe it for debilitated patients in the Eden Hospital, but its effect on these patients was not studied scientifically.

Intramuscular injections of whole blood (20 c.cm.) repeated every other day, or repeated small transfusions for a month, may improve the blood in the first half of pregnancy. (1925 to 1926 on ten cases only).

Repeated small transfusions are advantageous, particularly in the *moffussil* where they can be given without blood grouping. Col. Green-Armytage tried this method and none of his cases showed any untoward effect.

Intravenous blood transfusion in most of our cases in the Eden Hospital set up strong uterine contractions ending in premature labour.

Artificial interruption in the third trimester is invariably attended with some degree of sepsis. If the patient is left alone, pregnancy usually terminates spontaneously by premature labour.

Liver treatment and blood transfusion undoubtedly give better results *after* the termination of pregnancy.

Summary

(*i*) Pregnancy anæmia is not a disease entity but a syndrome-complex.

(*ii*) The symptom-complex of pregnancy anæmia is a manifestation of pathological changes in the different tissues as evidenced by hæmosiderosis, erythrophagocytosis and increase of cells of the reticulo-endothelial system and foci of myeloid changes in spleen and liver.

(*iii*) Defective hæmatopoiesis is due to the factors of (*a*) inadequate nutrition, (*b*) social and environmental conditions, (*c*) lack of antenatal care, (*d*) pre-existing anæmia and a possible defect in the blood-forming organs following anæmia, caused by tropical diseases. One or other, or a group of them in a condition like pregnancy upset the balance of the hæmapoietic system and abnormal corpuscles are thrown into the circulation, to be destroyed by the reticulo-endothelial cells which are increased in this condition.

(*iv*) Primiparæ suffer most, but the severity of the anæmia is not affected by age or parity.

(*v*) On the other hand nutrition and the mode of living, social and economic conditions, and early antenatal care markedly influence the severity of the anæmia. It is not so much the poverty but the injudicious dieting which is important.

(*vi*) There is an underlying sepsis, probably from the intestine by a quantitative increase of bacterial contents and their extension to usual sites. No particular bacterium is responsible for this. General leucocytosis with relative increase of neutrophiles is an evidence of sepsis.

(*vii*) Hæmatological and histopathological findings in pregnancy anæmia are similar to those of the 'pernicious anæmia' of Combe-Addisonian type. Leucopænia is absent in the majority of our cases of pregnancy anæmia.

Acknowledgments

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My indebtedness is also due to Major G. Shanks, M.D., I.M.S. (retired), Professor of Pathology, Medical College, Calcutta, for allowing me to carry out my researches and also for the valuable help I have received from him. I take this opportunity of also thanking Lieut.-Col. J. C. H. Leicester, F.R.C.P., F.R.C.S., I.M.S. (retired), for the encouragement I have received from him. My thanks are to Dr. A. Ganguli, M.B., who worked with me as Assistant Clinical Pathologist.

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CLINICAL STUDIES IN MALARIA BY CULTURAL AND ENUMERATIVE METHODS. SECOND SERIES

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In two previous papers (Knowles and Das Gupta, 1930, 1931) we have drawn attention to the value of cultural and enumerative methods in the clinical study of malaria. Since the publication of our 1931 paper these studies have been continued, and in the present paper we propose to give details of 23 selected further cases which are of interest, adopting consecutive serial numbering from the former paper. For purposes of classification it will probably be best to divide the cases concerned according to the species of parasite responsible. In order to save space, we shall adopt a tabular form for details wherever possible.

Infections with Plasmodium vivax. 6 cases

Case 16. *Low grade infection. Spontaneous cure.*—Kamala, Indian Christian, male child, aged 6 years, admitted on 18th January, 1932, with a history of fever for ten days. Spleen and liver not palpable. Temperature 98.8°F.

20th January. Afebrile. Parasite count 40 per c.mm.—rings.

21st January. Afebrile. Parasite count 80 per c.mm.—rings and trophozoites.

22nd January to 9th February. Afebrile. No parasites seen in thin and thick films.

9th February. Bass culture sterile.

Case 17. *Spontaneous cure with very rapid disappearance of gametocytes from the peripheral circulation.*—Mrs. S., Anglo-Indian, aged 22. Was treated for kala-azar four years previously and cured. History of fever with rigors for five days. Admitted 28th January, 1932. Spleen and liver not palpable. Parasite count, total 6,600 per c.mm., of which 1,800 per c.mm. are gametocytes. Temperature 98°F.

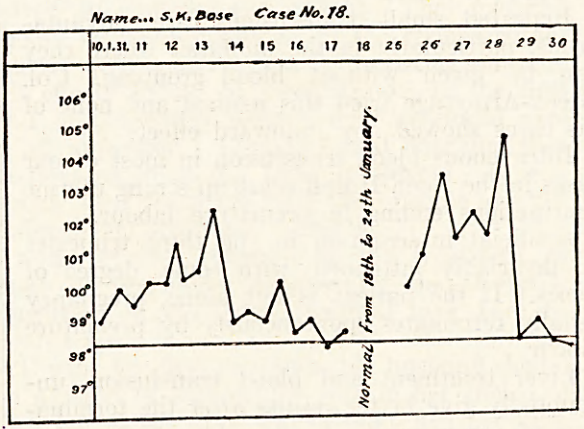
29th January. Temperature 99.2°F. Parasite count 80 gametocytes per c.mm.; no asexual forms seen.

30th January to 15th February. Afebrile. No parasites seen in thin and thick films.

15th February. Bass culture sterile.

Note.—The very rapid disappearance of gametocytes from the peripheral blood in this case is noteworthy. The duration of life of gametocytes of *P. vivax* in the peripheral blood (unless taken in by a transmitting anopheline) is probably only a matter of a few days.

CHART I



Case 18. *Experimentally induced benign tertian malaria. Spontaneous cure.*—S. K. Bose, Hindu male adult, admitted 13th December, 1930, with glosso-pharyngeal spasm. States that he had an attack of malaria about a month previously, but thin and thick films show no parasites. It was decided to induce malaria from a therapeutic point of view, and he was given 1/4 c.cm. of blood from a patient with benign tertian malaria on 23rd December.