IRON METABOLISM IN PREGNANCY

BY

ARNOLD KLOPPER, M.B., Ch.B., B.Sc.
D.Obst.R.C.O.G.

*Junior Registrar, Department of Obstetrics and
Gynaecology, Postgraduate Medical School
of London, W.12*

AND

S. VENTURA, M.B., B.S.

*Research Student, Department of Pathological Chemistry,
Postgraduate Medical School of London, W.12*

Haematological findings in the pregnant woman are difficult to assess. In the non-gravid state the normal range of variation in cell count and haemoglobin level is already generous. In pregnancy this range has to be increased and the scatter of values about the mean becomes widely dispersed. Not only may individuals vary widely from the arbitrary normal, but considerable changes may take place in the same individual in a short time. In part the difficulty arises from the increase in plasma volume during pregnancy, which Dieckmann and Wegner demonstrated in 1934. This means that cellular and haemoglobin concentration per unit volume will change without altering the essential feature which we wish to assess—the total oxygen-carrying capacity of the blood. For this reason it would seem desirable to calculate the total circulating cell mass and total haemoglobin in assessing a pregnancy anaemia. Modern methods of determining blood volume, such as the Evans blue technique used by Thomson *et al.* (1938) or the agglutination method of Mollison *et al.* (1943), are reasonably accurate, but are laborious and require so much skill and care as to put them beyond consideration as routine procedures.

The blood picture in pregnancy is further confused by other established physiological changes. The leucocytes are increased (Gibson, 1937), the red-cell fragility is increased (Elliott, 1944), and so is the erythrocyte sedimentation velocity (Whitby and Britton, 1950). The plasma proteins fall (Ward and MacArthur, 1947), and so does the prothrombin level (Javert and Macri, 1941).

Also during pregnancy there are several new factors which tend to produce anaemias of various types. Foetal demands for iron strain the mother's capacity to metabolize this metal. Pregnancy is sometimes associated with a deficiency of hydrochloric acid in the gastric juice (Strauss and Castle, 1932, 1933), which leads to defective iron absorption. The capricious appetite of a pregnant woman may produce dietary idiosyncrasies whereby the intake of iron-containing foodstuffs is inadequate. Bethell *et al.* (1939) have shown the necessity of adequate dietary protein for normal haemopoiesis. Protein lack is common in many parts of the world, and the increased protein need of pregnancy is often the precipitating factor of an anaemia. Pregnant women are particularly exposed to the risk of haemorrhage, and are prone to such anaemia-producing conditions as the vomiting of pregnancy and toxæmia.

Clearly it is most difficult to assess the haematological state of a woman just when she is peculiarly liable to defects of haemopoiesis. In this context it seemed worth while to consider the blood picture of the pregnant woman in terms of her iron metabolism rather than of

cellular production. Naturally this views only one facet of haemopoiesis, but it would be of interest if a description of this could be given. With this end in view we considered some of the literature on iron metabolism. The discovery of serum iron by Abderhalden (1898) was the starting-point for much valuable research into iron metabolism. As techniques were refined, workers in Europe and America were able to map out the physiological and pathological variations of this iron fraction. During the last decade the iron carrier has been identified as a specific subfraction of the β_1 globulins of the serum proteins. The use of radioactive iron isotopes as tracers by Hahn *et al.* (1940) and Granick's (1946) explanation of the mechanism of iron transfer to the blood stream from the intestinal lumen have further advanced our knowledge. We are approaching an understanding of the interrelationship of the metabolism of iron and copper.

Investigations into the iron metabolism of pregnancy have, however, been patchy and the results contradictory. During 1950 an investigation was undertaken to determine the normal levels, at various stages of pregnancy, of serum iron, the iron-binding capacity of the serum, the serum copper, and the free erythrocyte protoporphyrin in patients attending the antenatal service of Hammersmith Hospital (Ventura and Kloppe, 1951a). In the course of these investigations some anaemias of pregnancy were discovered. Similar determinations in these cases showed a picture differing from the normal. The purpose of the present communication is to present a study of these cases and to trace the regeneration of the picture when intravenous iron is given.

Material

The patients attending the antenatal department of this hospital were haematologically assessed by Professor G. A. Elliott in 1944, and by Professors Young, King, *et al.* in 1946. As the type of population has remained the same, we assumed that we were dealing with a group whose characteristics were known. In deciding whether any particular case was anaemic or not, we compared the findings to the standards set up for this population by these workers, as well as with the general standards proposed by Whitby and Britton.

All pregnant women attending the department have a routine haemoglobin estimation done at their first visit—generally when between 10 and 16 weeks pregnant. A repeat estimation is performed at 36 weeks. Any case having a haemoglobin of less than 10 g. of haemoglobin per 100 ml. (68% Haden) was brought under review. A red-cell and white-cell count was done, the packed cell volume and erythrocyte sedimentation rate were determined, and a stained film was examined. The usual indices were calculated—mean corpuscular volume, mean corpuscular haemoglobin, and mean corpuscular haemoglobin concentration. Any women found to have signs suggestive of anaemia during the course of routine antenatal care were similarly investigated. We were able in this manner to identify 43 cases of iron-deficiency anaemia among the 1,804 cases delivered by the obstetric service of the hospital.

Techniques

Haemoglobin estimations were done by the alkaline-haematin method of Wu (1922) as recommended by Clegg and King (1942). The colour intensity was read

with a photoelectric photometer against a standard of artificial haematin. Serum iron was determined by using potassium thiocyanate. We found this reagent to be more sensitive than alpha-alpha-dipyridyl and ortho-phenanthroline, which are sometimes used. Our method for determining serum iron is discussed in detail elsewhere (Ventura and Kloppe, 1951a).

Serum-copper determinations were made according to the method described by Cartwright *et al.* (1945); modified by using a simple 6/N hydrochloric acid extraction to free the copper from the serum proteins instead of the longer method using trichloroacetic acid.

The unsaturated iron-binding capacity of the serum is measured by determining the amount of iron which the serum proteins are capable of binding. Our method has been detailed elsewhere (Ventura, 1951).

The free erythrocyte protoporphyrin was determined according to the method of Grinstein and Wintrobe (1948).

Results

In 54 cases a haemoglobin level below 10 g.% was found. Some of these were very close to the critical level and on repeat examination were just above it. Such cases were put on oral iron therapy and kept under observation. If no further deterioration occurred we regarded them as low normals; eight cases were discarded in this manner.

Among the remaining 46 cases no examples of pernicious anaemia or other macrocytic anaemias were found. Reid and Mackintosh (1937) did not find any cases of pernicious anaemia in 1,108 pregnancies, and it is now generally accepted that in this country macrocytic anaemias rarely occur in pregnant women. Three cases were found to have haemolytic anaemias. One of these was a case of congenital haemolytic anaemia of obscure origin which had been under observation in the haematology department for many years and in which the pregnancy was incidental. The other two were mild cases of familial acholuric jaundice.

The remaining 43 cases were anaemias caused by disorders of iron metabolism. We found that these cases fell into two categories. The majority were classical cases of microcytic hypochromic anaemia. As we show later, biochemical analysis displayed a marked iron deficiency. This was readily corrected by the intravenous administration of iron. A smaller group (five cases) showed an aberrant pattern. Their red-cell counts fell *pari passu* with the reduction in haemoglobin, so that the colour index remained near unity; stained films presented a normochromic appearance and the cell size was not reduced. Further evidence of abnormal haemopoiesis was shown by an increased anisocytosis.

Normocytic Anaemia

The haematological findings of these five cases of normocytic anaemia are detailed in Table I. Bone-marrow smears prepared from two of the cases showed a normoblastic reaction. None of these patients complained of any symptoms suggesting anaemia, nor did they present any signs of the disease when examined. In all cases the pregnancy was well advanced, between 30 and 40 weeks. Previous investigations (Ventura and Kloppe, 1951a) have shown that in patients attending this department the normal level of serum iron is 72 μg . at this stage of pregnancy. The mean of these five cases is 71 μg . and all are well within the range of normal variation.

TABLE I.—*Normochromic Anaemias*

Case	Age	Parity	Maturity	Hb	R.B.C.	C.I.	M.C.V.	S.I.	I.B.C.	Cu	Porp.
A	35	6	40 wks.	9.8	3.4	1.0	88.5	81	343	173	21
B	27	1	38 "	9.6	4.0	0.85	78.2	71	315	245	25
C	40	0	33 "	9.5	3.7	0.90	80.2	68	235	142	32
D	33	3	34 "	9.8	3.6	0.96	84.1	69	395	197	38
E	30	0	36 "	9.5	3.4	0.98	86.3	65	290	165	71

Hb = Haemoglobin in grammes per 100 ml. R.B.C. = Red blood corpuscles in millions per c.mm. C.I. = Colour index. M.C.V. = Mean corpuscular volume in cubic microns. S.I. = Serum iron in μg . per 100 ml. I.B.C. = Iron-binding capacity in μg . per 100 ml. Cu = Serum copper in μg . per 100 ml. Porp. = Free erythrocyte protoporphyrin in μg . per 100 ml.

In like fashion the other constituents show normal levels when compared with the established values.

The values for normal pregnancy at 30–40 weeks we found to be: unsaturated iron-binding capacity, 382 μg ; serum copper, 255 μg ; protoporphyrin, 48 μg . It is presumed that these figures indicate that adequate transport iron is available for haemopoiesis and that the block in haemoglobin synthesis exists in iron utilization rather than in its absorption. Very little benefit can be expected from iron administration either orally or intravenously.

The diagnosis of anaemia is difficult to establish in these cases. It is not clear how much allowance should be made for the hydraemia of pregnancy in the individual case. Various authorities have put forward different minimal normal haemoglobin values for pregnancy (Dieckmann and Wegner, 1934; Adair *et al.*, 1936; Boycott, 1936; Bethell, 1936; Labate, 1940). Boycott in his paper stressed the importance of increased anisocytosis in the diagnosis of anaemia during pregnancy. This point was again emphasized by Elliott in working on material from this clinic. All five of the cases under discussion showed this characteristic. It may be, of course, that these borderline cases should be regarded as falling within the range of normal variation. We are concerned largely with the fact that the biochemical analyses show that these are not cases of deficient iron absorption, and that they are therefore not suitable for iron therapy.

Hypochromic Anaemia

The comparable findings in nine cases of hypochromic anaemia are summarized in Table II. Here the picture is quite different. The serum iron falls to a very low

TABLE II.—*Hypochromic Anaemias*

Case No.	Age	Parity	Maturity	Hb	R.B.C.	C.I.	M.C.V.	S.I.	I.B.C.	Cu	Porp.
1	20	0	26 wks.	10	4.2	0.83	76	47	545	181	112
2	25	1	30 "	8	4.2	0.67	66	29	464	202	171
3	35	2	34 "	8.6	4.0	0.75	75	21	470	170	162
4	32	1	24 "	9.0	4.6	0.69	67	37	437	307	106
5	27	0	28 "	7.4	3.6	0.72	70	26	512	308	191
6	41	3	28 "	5.7	3.4	0.59	59	27	540	352	77
7	29	2	26 "	9.4	3.8	0.87	71	40	470	351	86
8	43	3	30 "	9.8	4.1	0.84	70	28	538	291	42
9	33	6	28 "	8.3	4.8	0.61		37			95

See notes to Table I.

level. The iron-binding capacity of the serum proteins is considerably increased, and the level of serum copper rises above normal limits. As there is insufficient iron to combine with all the available protoporphyrin, the amount of free erythrocyte protoporphyrin is considerably raised. The picture of manifest iron deficiency

is corroborated by the haematological findings. The aetiology of these anaemias is often obscure. Our cases suggested several possibilities. Cases 1 and 4 were achlorhydric, Case 8 had a history of heavy blood loss with previous confinements, and Case 9 was a multi-gravida. Cases 2, 4, and 6 were poor women living in overcrowded homes on a monotonous impoverished diet.

Whatever the cause of the iron impoverishment may be in the individual case, all responded in a satisfactory manner to the intravenous administration of iron. By this means all the faults in the mechanisms of iron metabolism below the level of utilization are short-circuited. As can be seen in Table III, the anaemia is

TABLE III.—Response to Intravenous Iron

Case No.	Stage in Treatment	Hb	S.I.	I.B.C.	Cu	Porp.
1	Before commencement	10 g.	47	545	181	112
	After 100 mg. iron	10.2	50	561	200	127
	After 500 " "	12 g.	74	460	210	96
2	Before commencement	8.0	29	464	202	171
	After 100 mg. iron	8.5	35	471	200	169
	After 700 " "	10.2	63	420	210	—
3	" 1,000 " "	12.0	68	390	240	142
	Before commencement	8.6	21	470	170	162
	After 200 mg. iron	9.1	25	470	166	184
4	" 300 " "	10.2	42	410	150	102
	" 500 " "	11.2	41	432	142	131
	Before commencement	9.0	37	437	307	106
5	After 400 mg. iron	11.6	35	440	299	150
	" 600 " "	11.8	49	400	270	161
	Before commencement	7.4	26	512	308	191
6	After 100 mg. iron	8.0	30	475	320	251
	" 300 " "	8.9	45	412	278	240
	" 700 " "	10.5	58	420	260	180
7	Before commencement	5.7	27	540	325	77
	After 800 mg. iron	7.5	48	535	300	120
	" 1,300 " "	9.5	61	440	205	104
8	" 1,500 " "	9.7	74	400	185	105
	" 1,700 " "	14.5	82	395	155	105
	Before commencement	9.4	40	470	351	86
9	After 100 mg. iron	10.5	32	500	280	63
	" 400 " "	10.5	48	475	250	107
	Before commencement	9.8	28	538	291	42
10	After 100 mg. iron	10.4	51	450	295	99
	" 500 " "	11.6	59	448	280	75
	" 900 " "	13.5	72	336	171	101

See notes to Table I.

corrected irrespective of whether it be due to depleted iron reserves, dietary shortcoming, or a breakdown in iron absorption. This table shows the state of iron balance in eight cases at various stages of their recovery when treated with weekly injections of 100 mg. of "ferrivenin." Case 9 is not shown, as her veins were unsuitable and the treatment had to be abandoned after two injections. All the other cases received between 500 and 2,000 mg., treatment being continued until their haemoglobin rose above 10.2 g.% at a minimum. Reticulocyte counts done after the second injection revealed a response of 3%–9%. Clinically the patients showed improvement; pallor improved, and such symptoms as breathlessness and giddiness were relieved. Serum-iron levels rose slowly to normal, while the iron-binding capacity of the serum and the serum copper fell from their abnormally high concentration. In the case of protoporphyria the response was slow and uncertain. In general the trend was often downward, toward levels pertaining in normal pregnancy, but the pattern was not consistent.

The effect of ferrivenin on the regeneration of haemoglobin in the hypochromic anaemia of pregnancy was studied in a further 27 cases. The results are summarized in Table IV. The adult male is haematologically stable.

TABLE IV.—Effect of Intravenous Iron on Haemoglobin Level

Case No.	Initial Haemoglobin (g.)	Total Iron Given (mg.)	Final Haemoglobin (g.)	Rise per 100 mg. Iron (g.)
10	6.5	1,000	12.1	0.560
11	9.2	600	11.7	0.417
12	8.7	900	11.0	0.256
13	9.0	1,300	12.0	0.231
14	8.7	300	10.5	0.600
15	9.6	300	10.9	0.433
16	8.7	700	12.8	0.586
17	9.5	200	10.4	0.450
18	9.3	300	11.2	0.633
19	9.6	1,000	12.2	0.260
20	9.0	300	10.5	0.500
21	9.9	500	11.1	0.240
22	7.3	700	11.0	0.529
23	8.6	600	12.1	0.583
24	9.6	500	11.6	0.400
25	9.6	500	12.5	0.580
26	7.3	1,100	10.7	0.309
27	8.9	900	11.0	0.233
28	9.3	700	11.5	0.314
29	8.7	400	10.6	0.475
30	9.0	300	10.7	0.567
31	9.4	500	11.5	0.420
32	6.6	800	11.0	0.550
33	9.3	600	11.3	0.333
34	8.4	800	10.7	0.288
35	8.6	500	11.5	0.580
36	9.9	200	10.4	0.250

If given intravenous iron for an iron-deficiency state the injected iron will be quantitatively utilized. The expected rise in haemoglobin can be predicted with reasonable accuracy (Goetsch *et al.*, 1946). Simple haemoglobin estimations are an eminently satisfactory check on progress. If they do not correspond to predicted values some error in diagnosis or laboratory procedure has to be sought for. It is possible in these cases to calculate iron requirements accurately and so avoid overdosage with the possible danger of haemosiderosis. In the pregnant woman this state of affairs does not apply. The demands of the foetus for iron, and the hydraemia of pregnancy, introduce two new variables which make accurate forecasting of haemoglobin levels impossible.

Heath *et al.* (1932) have shown that in the non-pregnant state 24.5 mg. of iron is needed to raise the haemoglobin by 1% Haldane (0.16 g.) per day. On this basis a 100-mg. ampoule of ferrivenin should raise the haemoglobin by 4% (0.64 g.). Govan and Scott (1949) found that in pregnant women the highest response they obtained was 2.6% Haldane (0.416 g.), and they calculated that it would require nearly 40 mg. of ferrivenin to raise the haemoglobin by 1%. Our haemoglobin percentages were calculated on the Haden scale of 100% = 14.8 g., but, translating our values into Haldane equivalents, it can be calculated from the 35 cases in Tables III and IV that our average rise of haemoglobin per 100 mg. of iron was 2.7% (0.436 g.). By this calculation it would require 37 mg. of elemental iron to raise the haemoglobin of our cases by 1% Haldane.

We have published elsewhere a study of the urinary excretion of ferrivenin (Ventura and Klopfer, 1951b). We found that only 3.5% of the iron injected is lost. Evidently the discrepancy between anticipated rise in haemoglobin and the rise actually found is due to iron loss to the foetus. On the basis of our calculations 12.5 mg. of each 37 mg. of iron injected went to the foetus. Naturally this figure applies only in the last quarter of pregnancy, when foetal demands are high.

Summary

In late pregnancy iron-deficiency states are difficult to assess by ordinary haematological investigations. The levels

of serum iron, the iron-binding capacity of the serum proteins, the serum copper, and the protoporphyrin were investigated in normochromic anaemia and in hypochromic anaemia. In true iron-deficiency states these show a characteristic pattern which is quite different from the normal. This characteristic pattern was outlined in nine cases of microcytic hypochromic anaemia, and the regeneration towards normal was studied when these cases were given intravenous iron.

We are indebted to Professor James Young and Professor E. J. King for access to their patients and for the facilities to do this work. One of us (S.V.) is receiving a British Council grant. Mr. T. Simmonds kindly carried out all the haemoglobin determinations and cell counts.

REFERENCES

- Abderhalden, E. (1898). *Z. physiol. Chem.*, **25**, 65.
 Adair, F. L., Dieckmann, W. J., and Grant, K. (1936). *Amer. J. Obstet. Gynec.*, **32**, 560.
 Bethell, F. H. (1936). *J. Amer. med. Ass.*, **107**, 564.
 — Gardiner, S. H., and MacKinnon, F. (1939). *Ann. intern. Med.*, **13**, 91.
 Boycott, J. A. (1936). *Lancet*, **1**, 1165.
 Cartwright, G. E., Jones, P. J., and Wintrobe, M. M. (1945). *J. biol. Chem.*, **160**, 593.
 Clegg, J. W., and King, E. J. (1942). *British Medical Journal*, **2**, 329.
 Dieckmann, W. J., and Wegner, C. R. (1934). *Arch. intern. Med.*, **53**, 353.
 Elliott, G. A. (1944). *J. Obstet. Gynaec. Brit. Emp.*, **51**, 198.
 Gibson, A. (1937). *Ibid.*, **44**, 500.
 Goetsch, A. T., Moore, C. V., and Minnich, V. (1946). *Blood*, **1**, 129.
 Govan, A. D. T., and Scott, Jean M. (1949). *Lancet*, **1**, 14.
 Granick, S. (1946). *Chem. Rev.*, **38**, 379.
 Grinstein, M., and Wintrobe, M. M. (1948). *J. biol. Chem.*, **172**, 459.
 Hahn, P. F., Bale, W. F., Ross, J. F., and Whipple, G. H. (1940). *J. exp. Med.*, **71**, 731.
 Heath, C. W., Strauss, M. B., and Castle, W. B. (1932). *J. clin. Invest.*, **11**, 1293.
 Javert, C. T., and Macri, C. (1941). *Amer. J. Obstet. Gynec.*, **42**, 415.
 Labate, J. S. (1940). *Ibid.*, **39**, 87.
 Mollison, P. L., et al. (1943). *Lancet*, **1**, 637.
 Reid, W. J. S., and Mackintosh, J. M. (1937). *Ibid.*, **1**, 43.
 Strauss, M. B., and Castle, W. B. (1932). *Amer. J. med. Sci.*, **184**, 655.
 — (1933). *Ibid.*, **185**, 539.
 Thomson, K. J., Hirsheimer, A., Gibson, J. G., and Evans, W. A. (1938). *Amer. J. Obstet. Gynec.*, **36**, 48.
 Ventura, S. (1951). *Biochem. J.* In press.
 — and Klopfer, Arnold (1951a). *J. Obstet. Gynaec. Brit. Emp.*, **58**, 173.
 — (1951b). *Lancet*. In press.
 Ward, C. V., and MacArthur, J. L. (1947). *Trans. Amer. Ass. Obstet. Gynec. abstr. Surg.*, **58**, 142.
 Whitby, L. E. H., and Britton, C. J. C. (1950). *Disorders of the Blood*, 6th ed., pp. 123, 286. Churchill, London.
 Wu, H. (1922). *J. Biochem., Tokyo*, **2**, 173.
 Young, J., King, E. J., Wood, E., and Wootton, I. D. P. (1946). *J. Obstet. Gynaec. Brit. Emp.*, **53**, 251.

A note in the *New York Times Supplement*, November 4, describes some American experience with the new way of killing rats and mice with "warfarin." This contains dicoumarol, the blood anticoagulant often used in the treatment of thromboses, which was introduced for pest control by J. A. O'Connor in Malta in 1947. The anticoagulant is presented in the form of a food bait which is eaten fairly readily by animals over a period of time: internal bleeding occurs in 5 to 14 days, and they die from anaemia and shock, particularly if their normal blood volume is small, as is the case in rats and mice. The risk to pets is slight—a cat would have to eat several poisoned mice daily for at least a week to suffer ill-effects, while on farms the greatest danger is to hogs. There are estimated to be at least 300 million rats in the U.S.A., and one extremely successful rat-killing campaign in Texas is mentioned where 15 lb. of warfarin destroyed 550 rats. It is suggested that research should be carried out on other anticoagulants, which may prove more effective than dicoumarol in waging biological warfare on rodents.

DIABETIC GANGRENE

BY

A. GRUNBERG, M.D.

Physician in Charge of Diabetic Centre

H. L. DAVIES, Ch.M., M.Ch.(Orth.), F.R.C.S.

Consulting Orthopaedic Surgeon

AND

J. L. BLAIR, M.D.

Medical Registrar

St. Catherine's Hospital, Birkenhead

There is still a tendency in many places to proceed at once to radical surgery in diabetic gangrene, mainly because it is felt that, as in senile gangrene, nothing less than amputation, usually of the above-knee type, will arrest the progress of the disease. It is our aim in this paper to show that conservative surgery has a very definite place in treatment, and that it will in most cases leave a useful limb with a minimum of disability.

Diabetic gangrene can be divided into two types: (1) those cases in which infection is the primary factor; and (2) those in which occlusive vascular disease is the exciting cause.

The former type is found among the younger patients and is much less common than senile diabetic gangrene. The arterial tree appears perfectly normal, and so are the pulsations throughout the limb. The gangrene is due to primary infection followed by secondary thrombosis of the digital vessels. Occasionally the condition is well advanced before the patient is seen, owing to the associated diabetic neuritis and its resultant hyposensitivity and loss of pain.

The treatment of these cases, no matter how advanced the gangrene may appear, is definitely conservative. If possible the sensitivity of the organisms should be determined in order to indicate the correct antibiotic and chemotherapeutic agents to be used, and x-ray examination is necessary to exclude the presence of suppurative arthritis or osteomyelitis of the phalanges and metatarsals. Surgical treatment is limited to complete excision of all gangrenous tissue and adequate drainage of the affected tissue planes.

These simple measures are usually effective and only in exceptional circumstances is amputation necessary. The diabetic condition demands very careful supervision owing to the profound disturbance of metabolic balance resulting from the infection, but we have found that stabilization takes place almost immediately the infection is controlled.

The latter type is that which occurs in elderly patients; in these, degenerative changes in the peripheral blood vessels lead to decreased vitality in the tissues and diminished resistance to apparently trivial infections. The diabetic condition is usually mild or moderate in degree and the insulin requirement often minimal; control by diet alone may be sufficient. It is in such cases that conservative treatment plays its most important part, especially where impaired myocardial and renal functions are present and may lead to post-operative complications. It has been our experience that limited surgery, aided by chemotherapy and antibiotics, will avoid the necessity for amputation in a large number of these patients. This experience is contrary to the not