taken together in the two surveys. A separate analysis for the three kinds of school is also given, but with few exceptions the differences between them were not large. A total of 14.6% of the teeth in 1947 were carious, whereas for 1950 the figure was 13.9%. Comparative figures for caries incidence in other groups of children are given.

Only small differences were found between the two surveys as regards the amount of caries in the different types of teeth, but in 1950 more upper incisors and fewer first molars were carious than in the first survey.

The amount of treatment (fillings and extractions) which the teeth had received is briefly considered. An overall reduction of 5% was noted in 1950 as compared with 1947.

Some degree of gingivitis was found to occur in 73.7% of the children examined in 1947 and in 85.1% of those seen in 1950. That this is a common finding in this age group is substantiated by figures for other surveys.

Tartar deposits were frequently found, and there appeared to be some relation between the amount of tartar and the incidence and extent of gingivitis.

We wish to thank the London County Council and Sir Allen Daley for permission to carry out the inspections, and we are much indebted to the head teachers and staffs of the schools for all the help they gave with the actual examinations. Our thanks are also due to Miss I. Allen, of the Medical Research Council's Statistical Department, for advice; and to the Medical Research Council for financing the work.

REFERENCES

Dean, H. T., Jay, P., Arnold, F. A., jun., and Elvove, E. (1941). *Publ. Hlth Rep., Wash.*, **56**, 761.
King, J. D. (1940). *Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 241.
—— (1945). *Dent. Rec.*, **65**, 9, 32, 55.
—— and Martin, W. J. (1951). *Brit. dent. J.*, **90**, 35, 63.
Klein, H., and Palmer, C. E. (1937). *Publ. Hlth Bull., Wash.*, No. 239.
—— —— and Knutson, J. W. (1938). *Publ. Hlth Rep., Wash.*, **53**, 751.
Mellanby, M. (1934). *Spec. Rep. Ser. med. Res., Coun., Lond.*, No. 191.
—— and Coumoulos, H. (1946). *British Medical Journal*, **2**, 565.
Schour, I., and Massler, M. (1947). *J. Amer. dent. Ass.*, **35**, 1.
Weaver, R. (1950). *Brit. dent. J.*, **88**, 231.

INTESTINAL MACROCYTIC ANAEMIA

BY

G. M. WATSON, D.Ph., M.B., B.S., M.R.C.P.*

AND

L. J. WITTS, M.D., F.R.C.P.

(From the Nuffield Department of Clinical Medicine, the Radcliffe Infirmary, Oxford)

The occasional association of pernicious anaemia with intestinal stricture was discovered by Faber in 1895. In the succeeding years more cases were recorded, and in 1924 Seyderhelm and his associates claimed to have reproduced the syndrome in dogs. In 1929 Little, Zerfas, and Trusler found a blood picture typical of pernicious anaemia in a young man on whom several operations had been performed to cure an intestinal fistula which followed acute appendicitis. This appears to be the first record of pernicious anaemia in association with intestinal anastomosis as distinct from stricture. Other cases of this kind have since been reported, and the lesion has usually been either a gastro-jejuno-colic fistula or a stagnant loop of intestine. Tönnis *et al.* (1932) reported a brilliant series of experiments on culs-de-sac of the small intestine in dogs, and showed that the anaemia which sometimes developed would respond to liver extract.

*Australian National University Research Fellow.

In 1939 Barker and Hummel reviewed 51 cases of human pernicious anaemia associated with intestinal stricture or anastomosis, and we later brought the total to 60 (Cameron, Watson, and Witts, 1949a). In these 60 case reports anastomosis was the basic abnormality in 23, while in 37 one or more strictures were present. The strictures were mostly of the small intestine, but six were in the colon. Of the anastomoses 14 were entero-enterostomies or entero-colostomies, and nine were gastro-colic or high jejuno-colic fistulae.

The syndrome of gastro-colic fistula is now well known, its principle features being diarrhoea, steatorrhoea, malnutrition, and anaemia. Renshaw and his co-workers (1946) have made a careful clinical and experimental study of this condition. Dogs in which a gastro-colic fistula was made by operation developed a syndrome similar to that seen in man, including anaemia which in some cases became macrocytic and hyperchromic. In the dogs and in human cases it could be shown that there was little passage of gastric contents to the large bowel, and consequently the symptoms could not simply be due to diversion of food from the small intestine; rather were they due to contamination of the stomach and small intestine by colonic matter. In the cases of anaemia associated with stricture or anastomosis the fundamental abnormality appears to be the presence of a stagnant or obstructed portion of small intestine. All these mechanisms may lead to infection of the small intestine with colonic organisms.

Prominent Features

The salient features of pernicious anaemia in association with intestinal stenosis or anastomosis can be briefly enumerated. The tongue is often sore, but there is free acid in the gastric juice in more than half the cases. Intrinsic factor has been demonstrated in one case (Schlesinger, 1933), although it was absent in the only other case in which it was looked for (Castle *et al.*, 1931). Steatorrhoea is not necessarily present, but there have been few careful observations on the fat excretion. Subacute combined degeneration occurs in a fairly large proportion of cases. The bone marrow is megaloblastic, and the anaemia, which is macrocytic, responds to treatment with liver, though it is sometimes rather resistant. No information is available about the response to vitamin B_{12}, folic acid, or antibiotics. The anaemia may be permanently cured by surgical correction of the intestinal abnormality, though this cannot be promised with certainty. The syndrome has declined in frequency in recent years owing to the decreased incidence of intestinal tuberculosis, which has been the most frequent cause of stenosis of the small intestine, and to technical improvements in surgery, which avoid the formation of stagnant loops of intestine.

Present Investigation

The essential feature in macrocytic anaemia of intestinal origin appears to be stagnation, whether from stenosis or in a stagnant loop. The syndrome differs from Addisonian pernicious anaemia in that the secretion of hydrochloric acid and intrinsic factor by the stomach may be normal; and from sprue in that there need be no steatorrhoea. It seems particularly appropriate for experimental study because it is impossible to produce a megalocytic anaemia by operations on the stomach in animals (Cameron, Watson, and Witts, 1949b), and

pernicious anaemia does not always develop after total resection of the stomach in man (MacDonald *et al.*, 1947).

These observations led us to the working hypothesis that in pernicious anaemia the failure of gastric secretion might merely set the stage for the development of anaemia, which was actually initiated by events in the small intestine. With this idea we began a series of experiments with rats. We considered that the disadvantage of using so small an animal was outweighed by the ease with which we could make large numbers of preparations. A further point is that the diet and digestive tract resemble that of man, and we have been able to prepare extracts from rat livers which are effective in human pernicious anaemia. Adult albino rats of the Wistar strain, aged 4 to 6 months, have been used in all experiments. They have been fed on a synthetic diet (Watson, Cameron, and Witts, 1948), but anaemia will develop in animals receiving a mixed diet with plenty of animal protein (W. A. Broom, J. Emmet, and Woods, 1949, personal communication).

Experimental Technique

The initial experiments were designed to produce intestinal stricture and chronic obstruction, but although several methods were tried none was found satisfactory. The next procedure was to divide the small intestine at the junction of its upper and middle thirds and implant the lower end of the upper intestine into the side of the small intestine at the junction of the middle and lower thirds; in this way the middle third of the small intestine is by-passed. This operation is relatively easy to perform. Nearly 200 rats were prepared in this way, but only about 10% of them developed a macrocytic anaemia, and the proportion tended to lessen as the operators became more skilled. These experiments confirmed the results of other workers who had found that a large proportion of the small intestine can be removed or by-passed without anaemia resulting, and indeed the majority of the rats lived to a ripe old age. More important was the discovery that in rats which developed anaemia there was always some dilatation of the blind loop. In most cases this was limited to the proximal 6–10 cm. of the loop and the anastomotic area, but in a few there was also some dilatation of the small intestine above the anastomosis.

The Blind-loop Operation

It was therefore decided to reverse the direction of the blind loop so that now peristalsis would tend to fill instead of emptying it. This was done by dividing the small intestine at the junction of the middle and lower thirds, and anastomosing the lower portion to the side of the small intestine at the junction of its upper and middle thirds. The same segment of intestine was by-passed as in the earlier operation, but the effects were very different. The operation was technically more hazardous because peristalsis now tended to break down the anastomosis. The middle third of small intestine, aproximately 12 in. (30 cm.) long, increased in diameter and formed an easily palpable tumour. Three out of every four rats died within three weeks, but all those which survived for that time developed macrocytic anaemia.

Further experiment showed that the percentage of anaemic animals, the speed of onset of the anaemia, and the mortality of the operation were all directly proportional to the length of the loop. It was then a straightforward procedure to work out the optimum length and position of the loop. As a result of these studies all our subsequent work has been done with 3 to 4-in. (7.5 to 10-cm.) self-filling loops placed not lower than the middle of the small intestine. Culs-de-sac from the lower ileum usually fail to produce anaemia. The Table shows the overall operative and post-operative mortality of rats prepared by this final operation. It is necessary to point out that the incidence of anaemia varied considerably at different periods for no very obvious reason. Thus, in one set of experiments a yield of only a little over 10% of anaemic rats was obtained, while in another it was as high as 42%.

Operative Mortality and Incidence of Anaemia

Death within one month of operation	51·7%
Dying up to six months from later complications or unknown causes	21·6%
Surviving six months or more without anaemia ..	7·4%
Developing anaemia	19·1%

Deaths within the first month were mostly from leakage or obstruction. Obstruction or perforation still occurred frequently in the later period, but many rats died without the cause being apparent at necropsy.

Post-mortem Findings

At post-mortem examination of animals which have survived the immediate hazards of operation the wall of the cul-de-sac is dilated and hypertrophied, but there is no inflammation or ulceration save in the exceptional case in which rupture has occurred. The tongue, stomach, and the rest of the gut appear normal, as do the other viscera. Histological examination of all these structures shows no departure from the normal. There is some haemosiderosis of the spleen, but the liver and kidneys are normal. Because of the suggestion by Erös (1933) and Jacobson (1939) that the argentaffin cells of the gastro-intestinal tract are concerned in the pathogenesis of the liver-deficiency macrocytic anaemias in man, we paid special attention to these cells in our experimental material and found them normal in appearance, number, and distribution in the stomach and intestine (Cameron, Watson, and Witts, 1950). The nervous plexuses of the gut are normal and there are no abnormalities in sections of the spinal cord. We saw no clinical symptoms of nervous disease even in animals which had been kept alive with folic acid.

The culs-de-sac are usually filled with a thick, dark, liquid material. This consists mainly of the bodies of bacteria with little food residue or desquamated mucosa. The bacteriological findings are much as if the ordinary flora of the caecum had ascended to the loop and the ileum. In the ileum itself there is a great increase in coliform organisms, a decrease in lactobacilli, and a corresponding increase in alpha-haemolytic streptococci.

Post-operative Developments

After operation those rats which do not die from surgical complications in the first few weeks may remain apparently well for long periods. Anaemia develops, often quite suddenly, after an interval which averaged about 90 days in a large series of rats, the range being from 26 days to 6 months. Failure to develop anaemia is sometimes explained by the formation of fistulae or blocking of the loop by adhesions, and similar happenings may account for some of the occasional spontaneous remissions. Nevertheless some animals in which the anatomical stage is set for anaemia do not become anaemic. Quite apart from anaemia, the expectation of life is much diminished in operated rats,

and they not infrequently die for reasons which we do not understand. However, it will be seen from the Table that not many of the rats which survive the initial hazards of the operation will live for six months without developing anaemia. Anaemic animals are perceptibly pale and listless, and may lose weight, but do not show other evidence of disease unless they develop pyogenic infection, to which they are more susceptible than healthy animals. Death may follow within a week of the onset of anaemia, and life is rarely prolonged more than three weeks without treatment, though an occasional anaemic rat has lingered for months and others have had remissions and relapsed again.

The Blood

All blood counts have been done on tail blood, and we have collected a large number of normal data (Cameron and Watson, 1949). The normal haemoglobin of female rats, which we used in all except the earliest experiments, was 13.8 g. per 100 ml. We define anaemia as a haemoglobin value below 10 g., although many of our rats had fallen much below that level before coming under treatment. In a small control series of anaemic rats allowed to die without treatment the haemoglobin at death averaged 5.8 g. per 100 ml., with a range of 2.7 to 8.5 g. per 100 ml. Macrocytosis is always present. In determining the size of the red cells we have relied more heavily on the red-cell diameter, which is a direct measurement, than on the mean corpuscular volume, which includes two sources of error—the red count, and the haematocrit.

From a large series of Price-Jones curves we have established the normal distribution of the red-cell diameter in the rat for our particular technique. The limits of normal for the mean cell diameter in the female rat are 5.73 and 6.56 μ, with an average of 6.14 μ. The normal mean corpuscular volume is 49 μ^3. In anaemic animals the presence of macrocytosis is shown by increase in the mean cell diameter and volume, and by extension of the Price-Jones curve beyond the upper limits of normal. The figures in one small series of 10 anaemic animals averaged 6.62 μ for the mean cell diameter, with a range of 6.37 to 7.33 μ; and 55 μ^3 for the cell volume, with a range of 50 to 67 μ^3. The mean corpuscular haemoglobin is often but not invariably increased.

Macrocytosis is usually obvious in the stained film. Poikilocytosis is never more than slight. The anaemic animals have an irregular reticulocytosis, which may increase from the normal 4% to about 20% as the anaemia worsens, and which is manifested in the stained films by polychromasia. Nucleated red cells are seen in the peripheral blood in all but the lightest anaemias. Leucocytes are not reduced in numbers and they do not show any measurable qualitative change. Marrow smears taken in life show that the cellularity of the marrow is normal or increased (Watson, Cameron, and Witts, 1948). The most striking change is a shift to the left in the maturation of the red-cell precursors. In some cases the increase in proerythroblasts and large basophil erythroblasts is noteworthy, but no cells are seen which correspond exactly with the megaloblasts of human pernicious anaemia.

The serum is crystal-clear and therefore no estimation of serum bilirubin has been attempted. The amount of urobilinogen excreted in the faeces is significantly increased (Badenoch and Watson, 1951). As the normal daily excretion of urobilinogen roughly parallels the amount of haemoglobin in circulation, we have expressed our results in the form of the haemolytic index (Miller, Singer, and Dameshek, 1942). This is the figure obtained by dividing the daily excretion of pigment in milligrams by the total haemoglobin in grammes and expressing this fraction as a percentage. The haemolytic index in the anaemic rats is seven times as high as in the normals. Fat absorption was deficient in most of the operated rats, but many had steatorrhoea without anaemia and a small proportion developed anaemia without showing impaired absorption of fat. In this latter group there did not appear to be any sepsis or haemorrhage to explain the anaemia. Although, therefore, there is some correlation between anaemia and steatorrhoea, it is not absolute. It is probable that both steatorrhoea and anaemia are due to a common cause, and not that steatorrhoea causes the anaemia (Aitken, Badenoch, and Spray, 1950).

Latent Bartonella infection may be activated when rats with intact spleens are fed on deficient diets (Wills and Mehta, 1930), and it was therefore possible that our animals might have developed bartonellosis and anaemia as a result of nutritional deficiency produced by the intestinal lesion. Blood films from anaemic rats never showed the frank infection with Bartonella which is seen after splenectomy in susceptible animals. However, it is impossible to be sure of identifying small numbers of Bartonellae in stained blood films, and further work was necessary to be certain that the anaemia was not caused by bartonellosis. Two measures were taken. The first was to maintain, with rigorous precautions against infection, a stock of Bartonella-free rats. These animals were prepared by operation in the usual way and it was found that anaemia developed as in the earlier experiments. The second measure was to treat a series of anaemic rats with neoarsphenamine, to which *Bartonella muris* is sensitive, and it was shown that the anaemia was not relieved by this therapy (Watson and Witts, 1951a). It is reasonably certain, therefore, that the development of anaemia in these rats is not dependent on Bartonella infection.

Responses to Treatment

A purified liver extract ("anahaemin") was given by intramuscular injection in single doses of 0.1 to 0.4 ml. to 17 rats with macrocytic anaemia after the earlier and milder operation, the self-emptying loop. In 10 rats there was some response to liver, and of the remaining seven which died six had some complication such as infection or perforation. Some of these rats responded on three successive occasions to an injection of liver extract. Response is shown by a reticulocyte crisis, which must be assessed with caution owing to the irregular reticulocytosis produced by the anaemia, and, more significant, by a rise in the number of red cells and in the haemoglobin. Macrocytosis diminishes, though the red cells may not return completely to normal size. These results appeared to us convincing, but we have not been able to get consistent responses to liver treatment in rats prepared by our present more rigorous procedure.

In the next experiment the blood counts of rats which had been submitted to the standard operation—that is, the 3-in. (7.5-cm.) self-filling loop—were checked at weekly intervals, and anaemic animals were assigned in sequence to one of four groups. One of these was a control group, and the others were treated respectively with anahaemin, pteroylglutamic acid, and vitamin B_{12}.

High doses were used, as from early experience it had seemed that these were necessary. We had already found that supplementing the basic diet with 200 μg. of pteroylglutamic acid daily would not prevent anaemia developing, although this amount is well in excess of what is now thought to be the basal requirement (Darke and White, 1950). The material was given by injection three times a week in the following amounts : anahaemin, 0.5 ml.; pteroylglutamic acid, 7.5 mg.; and vitamin B_{12}, 20 μg. This experiment provided clear evidence in favour of pteroylglutamic acid, which prolonged the duration of survival to approximately 80 days as compared with 20 days in the controls. The effects of anahaemin and vitamin B_{12} were not significant statistically (Cameron, Callender, Watson, and Witts, 1949).

In a final therapeutic experiment a series of anaemic rats were treated with " aureomycin " incorporated into the basic diet. This was found to be as effective as folic acid in curing the anaemia and prolonging life in these rats (Watson and Witts, 1951b).

Discussion

A macrocytic anaemia which is usually fatal develops in a proportion of rats which have survived the operation for the formation of a blind loop in the small intestine. Most of these rats have also a mild steatorrhoea, but the correlation between anaemia and steatorrhoea is not absolute and the anaemia does not seem to be sequential to steatorrhoea. Anaemia is not an inevitable result of the operation, and cases of anaemia tend to occur in runs or crops, as if some common initiating factor appeared from time to time. This initiating factor may well be bacterial in nature—indeed, some of our evidence points to this—but it does not appear to be *Bartonella muris,* as the condition has been induced in a Bartonella-free stock and does not respond to neoarsphenamine. Owing chiefly to the high operative and post-operative mortality, the final yield of rats with anaemia is of the order of 20%, and in some series has been as low as 10%. It sometimes happens, therefore, that a fairly large consecutive series of rats are operated upon without anaemia developing. Nevertheless, this technique has been found to produce anaemia by other groups of workers (Broom, Emmet, and Woods, 1949, personal communication ; Jarman and Underhill, 1951), and a similar condition has been produced by excision of the caecum in the rat (Plum, 1950).

The anaemia is of a macrocytic haemolytic character with reticulocytosis and increased pigment excretion. The bone marrow shows a shift of erythropoiesis to the left, but cells comparable to the megaloblasts or pernicious anaemia in man or the primitive erythroblasts of the foetal rat are rarely seen. The anaemia usually responds well to folic acid but not to refined liver extract or to vitamin B_{12}. It also responds to treatment with aureomycin by mouth, and there is a suggestion in the work of Jarman and Underhill (1951) of a response to sulphaguanidine. The anaemia differs from the blood disorder produced in the rat by folic-acid deficiency, which is macrocytic without haemolytic features and in which leucopenia is more prominent than anaemia (Kodicek and Carpenter, 1950). Nor is it identical with the condition produced in the rat by folic-acid antagonists, where the bone marrow has usually been hypoplastic (Oleson, Hutchings, and Subbarow, 1948 ; Philips and Thiersch, 1949), though megaloblastic arrest has been reported once (Franklin *et al.,* 1947), as has also an active non-megaloblastic marrow (Weir, Heinle, and Welch, 1948). Thiersch and Philips (1949) point out that there are wide variations in the response of different species to folic-acid antagonists.

It is not easy to postulate the mechanism by which an intestinal cul-de-sac gives rise to anaemia in the rat, but there is sufficient evidence to permit limited speculation. We know that in these rats there is a bacterial invasion of the small bowel similar to that which occurs in people with gastro-colic fistula, and it is likely that the anaemia and steatorrhoea are similar in nature in the two conditions. The response to aureomycin, which may be presumed to check this invasion, is of particular interest in view of recent reports of the therapeutic value of aureomycin and penicillin in pernicious anaemia in man (Lichtman, Ginsberg, and Watson, 1950 ; Foy, Kondi, and Hargreaves, 1951) and the much older reports on the value of ileostomy in human pernicious anaemia (Seyderhelm, 1924 ; Dixon, Burns, and Giffin, 1925). These observations in rats and in man suggest that the intestinal bacteria have something to do with the absorption or the requirements of vitamin B_{12} and folic acid. Support for this view comes from the work of Davis and Chow (1951), who found that aureomycin increased the vitamin-B_{12} content of the faeces of rats given radioactive cobalt with their diet, measured by both radioactive and microbiological methods.

We have thought that when there is stenosis of the small intestine or a stagnant loop the decisive event in the production of anaemia may be a change in the flora of the loop or the small intestine. There are several ways in which this could lead to anaemia. It might cause the loss of an organism which synthesizes haemopoietic material, or the predominance of an organism which uses up haemopoietic material. It is possible that a toxin is formed which acts other than by interference with the production or absorption of haemopoietic materials. The rapid onset of vitamin-B deficiency in patients who have undergone total gastrectomy suggests that such ideas are not extravagant (Brain and Stammers, 1951), and the production of pernicious anaemia by the fish tapeworm in the small intestine is another parallel (von Bonsdorff, 1948).

It would clearly be desirable to test such ideas by experiment both in man and in animals. Unfortunately the difficulties of detailed microbiological studies in the intestine are considerable, and, owing to the high mortality and frequent post-operative complications, the rat with an intestinal cul-de-sac has not proved an entirely satisfactory pharmacological preparation. We have been unable to diminish the mortality and complications greatly by improvements in technique. They seem to be closely related to the small size of the rat, and it may be necessary to use a larger experimental animal if the anaemia of intestinal stenosis and anastomosis is to be studied further by animal experiment.

Summary

The well-known clinical association of megaloblastic anaemia with intestinal stricture and anastomosis suggested that an operation of this type might be used to produce macrocytic anaemia in an experimental animal.

The formation of a small intestinal cul-de-sac in the rat leads to macrocytic anaemia in a proportion of cases, provided that the cul-de-sac has stagnant contents and is placed in the upper part of the small intestine.

The anaemia is associated with haemolysis, and sometimes with steatorrhoea. It responds well to folic acid or aureomycin but poorly or not at all to vitamin B_{12}.

From the available evidence the most likely cause of the anaemia is an alteration of the intestinal flora analogous to that which occurs in cases of gastro-colic fistula in man, and it is possible that the intestinal bacteria are in some way concerned with the absorption or utilization of haemopoietic substances.

We wish to thank our collaborators, whose names are mentioned in the references, and we are indebted to the Medical Research Council for a grant for technical assistance and expenses.

REFERENCES

Aitken, M. A., Badenoch, J., and Spray, G. H. (1950). *Brit. J. exp. Path.*, **31**, 355.
Badenoch, J., and Watson, G. M. (1951). *J. Path. Bact.*, **63**, 523.
Barker, W. H., and Hummel, L. E. (1939). *Bull. Johns Hopk. Hosp.*, **64**, 215.
Brain, R. H. F., and Stammers, F. A. R. (1951). *Lancet*, **1**, 1137.
Cameron, D. G., Callender, S. T. E., Watson, G. M., and Witts, L. J. (1949). *Nature, Lond.*, **164**, 188.
—— and Watson, G. M. (1949). *Blood*, **4**, 816.
—— —— and Witts, L. J. (1949a). Ibid., **4**, 793.
—— —— —— (1949b). Ibid., **4**, 803.
—— —— —— (1950). *Brit. J. exp. Path.*, **31**, 349.
Castle, W. B., Heath, C. W., and Strauss, M. B. (1931). *Amer. J. med. Sci.*, **182**, 741.
Darke, S. J., and White, C. (1950). *Brit. J. Nutrit.*, **4**, 9.
Davis, R. L., and Chow, B. F. (1951). *Proc. Soc. exp. Biol., N.Y.*, **77**, 218.
Dixon, C. F., Burns, J. G., and Giffin, H. Z. (1925). *J. Amer. med. Ass.*, **85**, 17.
Erös, G. (1933). *Wien. klin. Wschr.*, **46**, 1119.
Faber, K. (1895). *Hospitalstidende*, **3**, 601.
Foy, H., Kondi, A., and Hargreaves, A. (1951). *British Medical Journal*, **1**, 380, 1108.
Franklin, A. L., Stokstad, E. L. R., Belt, M., and Jukes, T. H. (1947). *J. biol. Chem.*, **169**, 427.
Jacobson, W. (1939). *J. Path. Bact.*, **49**, 1.
Jarman, R. M., and Underhill, S. W. F. (1951). *J. Pharm. Pharmacol.*, **3**, 87.
Kodicek, E., and Carpenter, K. J. (1950). *Blood*, **5**, 522.
Lichtman, H., Ginsberg, V., and Watson, J. (1950). *Proc. Soc. exp. Biol., N.Y.*, **74**, 884.
Little, W. D., Zerfas, L. G., and Trusler, H. M. (1929). *J. Amer. med. Ass.*, **93**, 1290.
MacDonald, R. M., Ingelfinger, F. J., and Belding, H. W. (1947). *New Engl. J. Med.*, **237**, 887.
Miller, E. B., Singer, K., and Dameshek, W. (1942). *Arch. intern. Med.*, **70**, 722.
Oleson, J. J., Hutchings, B. L., and Subbarow, Y. (1948). *J. biol. Chem.*, **175**, 359.
Philips, F. S., and Thiersch, J. B. (1949). *J. Pharmacol.*, **95**, 303.
Plum, C. M. (1950). *Sang*, **21**, 437.
Renshaw, R. J. F., Templeton, F. E., and Kiskadden, R. M. (1946). *Gastroenterology*, **7**, 511.
Schlesinger, A. (1933). *Klin. Wschr.*, **12**, 298.
Seyderhelm, R. (1924). Ibid., **3**, 568.
—— Lehmann, W., and Wichels, P. (1924). Ibid., **3**, 1439.
Thiersch, J. B., and Philips, F. S. (1949). *Proc. Soc. exp. Biol., N.Y.*, **71**, 484.
Tönnis, W., Horster, H., Reimers, C., and Rüdel, C. (1932). *Z. ges. exp. Med.*, **84**, 782.
von Bonsdorff, B. (1948). *Blood*, **3**, 91.
Watson, G. M., Cameron, D. G., and Witts, L. J. (1948). *Lancet*, **2**, 404.
—— and Witts, L. J. (1951a). *J. Path. Bact.*, **63**, 526.
—— —— (1951b) In publication.
Weir, D. R., Heinle, R. W., and Welch, A. D. (1948). *Proc. Soc. exp. Biol., N.Y.*, **69**, 211.
Wills, L., and Mehta, M. M. (1930). *Indian J. med. Res.*, **18**, 663.

Nearly 800 new members were recruited in England and Wales to the National Hospital Service Reserve in November, bringing the total strength to 18,573. Of these, 1,706 are trained nurses and 16,839 nursing auxiliaries. Newcastle Hospital Region headed the November recruiting with 200 members, more than a quarter of the month's total of 796. Manchester came second with 102, and Bristol third with 94. Wales still has the largest total membership, 3,634, followed by the South-west Metropolitan Area with 2,277, and Newcastle with 1,643. A new recruiting drive was launched at the end of November by Miss Hornsby-Smith, Parliamentary Secretary to the Ministry of Health, with the aim of trebling membership and so bringing the Reserve well on the way to its peacetime objective of 80,000 members.

THE EFFECT ON BLEEDING-TIME OF AN EXTRACT OF BLOOD OF PATIENTS WITH RHEUMATOID ARTHRITIS

BY

RAYMOND GREENE, D.M., M.R.C.P.
Physician, Royal Northern and Metropolitan Hospitals

JOSEPHINE VAUGHAN-MORGAN, B.Sc.
Formerly Biochemist to the Phillip Hill Clinic at the Royal Northern Hospital

AND

JULIA GAMMON, B.Sc.
Formerly Deputy Biochemist to the Phillip Hill Clinic at the Royal Northern Hospital

It has for many years been a matter of discussion among those interested in the origins of rheumatoid arthritis that the disease may arise in apparent association with a large number of disturbing incidents, including infection, trauma, burns, excessive fatigue, the use of certain drugs, the metabolic crises of puberty, child-bearing, and the climacteric, and the psychological stresses and strains of normal life. That these incidents were the only cause was never believed, and statisticians who disproved to the hilt their sole significance might have excused themselves the labour of belabouring a donkey which had never lived.

Nevertheless, to experienced clinicians it was obvious that, though the majority of people could suffer with impunity the "slings and arrows of outrageous fortune," there were others who could not. Their interest was centred not on the hammer's stroke but on the anvil's ring, and was intensified by the description by Hans Selye (1936b, 1937) of the alarm reaction, which concentrated their attention upon the adrenal cortex. From the beginning it seemed likely, on clinical grounds, that the adrenals, if involved at all in the story of rheumatoid arthritis, would be found to be normal in this condition, for no evidence of adrenal deficiency had been observed in extensive investigations of the biochemistry of rheumatism. It seemed more likely that the error would be found in a mechanism in which the adrenal cortex served as an essential part, and that it would be in the control of the adrenals or in the response to the adrenals that the error would be found.

The Literature

Various Soviet authors (Synovich, 1940; Pshenichnikov, 1940; Novikov, 1941—reviewed by Clarke, 1941) claimed to have shown that the systemic use of local anaesthetics had resulted in a significant decrease in traumatic shock. Their results were confirmed by Ungar (1943), who found that "nupercaine" (cinchocaine) was especially effective. Extending his observations, Ungar (1944) found that several procedures were capable of protecting guinea-pigs and rats against subsequent trauma by causing an inhibition of histamine release. These procedures included the production of previous minor trauma and the administration of ascorbic acid, nupercaine, procaine, cocaine, adrenaline in unphysiological doses, a whole cortical extract prepared by Kendall, anterior pituitary extract, and, pre-eminently, adrenocorticotrophic hormone (A.C.T.H.). The protection afforded by these procedures (except the