South African Medical Journal : Suid-Afrikaanse Tydskrif vir Geneeskunde

EDITORIAL : VAN DIE REDAKSIE

PERNICIOUS ANAEMIA

We suggested recently[1] that iron deficiency should be considered on finding a low mean corpuscular haemoglobin concentration. It is not easy to obtain a reliable index for macrocytic anaemias since an accurate red-blood-cell count is required. A diagnosis of pernicious anaemia may be indicated on examination of a well-stained blood smear, since the presence of anisocytosis and macrocytosis and a tendency to ovalocytosis give a typical picture of the condition. However, since a diagnosis of pernicious anaemia implies life-long treatment, it is necessary to be sure of the diagnosis. The administration of vitamin B_{12} is seldom justified unless a positive diagnosis has been made.

Of the readily available tests, the examination of the bone marrow is the most satisfactory. Demonstration of megaloblastic erythropoiesis takes us a long way in making a diagnosis. If the anaemia is not severe, if a complication such as iron deficiency or infection is present, or if some treatment has been given, only 'intermediate megaloblasts' may be found. The megaloblasts are red-cell precursors—morphologically intermediate between normoblasts and the typical megaloblasts of classic pernicious anaemia.[2] The presence of abnormalities in the white cells, such as giant band myelocytes and mature polymorphs with multilobed nuclei, should also be taken as a sign of disordered haemopoiesis and raise a suspicion of deficiency of what used to be called the 'liver factor'. These abnormal white cells are commonly found in association with megaloblastic blood formation.

Blood for the calculation of the vitamin-B_{12} level in the serum must be taken before treatment is initiated, since the opportunity may never again be present; and in this way a vitamin-B_{12} deficiency state can be recognized with certainty. Unfortunately, the test is time consuming, costly, and not available except in special centres. To postulate such a vitamin-B_{12} deficiency state one has usually to be satisfied with a reticulocytosis and rise in haemoglobin following treatment with vitamin B_{12}.

Until recently, the final step in the diagnosis of the average case of pernicious anaemia had been the demonstration of achylia gastrica (this includes absence of both hydrochloric acid and pepsin). Secretion of free hydrochloric acid can be demonstrated by the use of the so-called 'tubeless' gastric analysis;[3] the demonstration of free hydrochloric acid in the gastric juice makes the diagnosis of true Addisonian pernicious anaemia very unlikely. If this test is negative a conventional test using histamine is necessary, for a stricter criterion for achlorhydria needs to be adopted. Card *et al.*[4] advocate the 'augmented histamine test'—a large dose of histamine is injected (the undesired side-effects are neutralized by an antihistaminic drug) and the gastric pH is then measured. These writers claim that only patients with pernicious anaemia are achlorhydric when tested in this way. On the other hand, using a gruel meal and a more conventional dose of histamine, Jacobs[5] found that many patients with pernicious anaemia secreted small amounts of hydrochloric acid—sometimes enough to reach a level of 'free acid'. This is in keeping with histological pictures of the gastric mucosa[6] which show that complete atrophy is not present in all cases of pernicious anaemia. Despite this, the test meal still remains a very important test for, while the absence of achlorhydria does not necessarily exclude the diagnosis, it makes it most unlikely.

A doctor may be faced with the problem of a patient who claims to have been diagnosed and treated as a case of pernicious anaemia. Since the patient would thus be receiving regular treatment with vitamin B_{12} he would not be anaemic and his bone marrow and serum vitamin-B_{12} level would be unlikely to be abnormal. An augmented histamine test, or even a gastric biopsy, could be performed; but neither of these tests provides unequivocal evidence of pernicious anaemia. It is preferable to perform tests utilizing radio-isotopes, which are now available and have proved very useful in practice. The efficacy of radio-isotopes depends on the inability of a patient with pernicious anaemia to absorb orally administered vitamin B_{12}. A small dose of vitamin B_{12} labelled with cobalt 60 (or cobalt 58) is given by mouth and the amount absorbed is estimated. This can be assessed either from the amount of vitamin B_{12} passed in the stool (assuming the patient has absorbed the difference between that and the dose he was given), or, perhaps more elegantly, by injecting a large 'flushing dose' of non-radio-active vitamin B_{12} two hours later. The bulk of the non-radio-active vitamin B_{12} injected will be excreted in the urine. The body is unable to discriminate between radio-active and non-radio-active vitamin B_{12}, and excretes an equivalent proportion of absorbed radio-active vitamin B_{12}; consequently measurement of radio-activity in the urine provides an easy method of assessing the amount absorbed. The amount absorbed can also be assessed by monitoring radio-activity over the liver after the patient has cleared the gastro-intestinal tract of vitamin B_{12} given by mouth. The test is repeated, the oral radio-active vitamin B_{12} being given together with a source of intrinsic factor. This should enable the patient with pernicious anaemia to absorb the vitamin.

By one or other of these tests with radio-active vitamin B_{12} the ability of the body to absorb an orally administered vitamin can be assessed, and by a suitable combination of tests it is possible to infer whether or not the patient secretes intrinsic factor. If intrinsic factor is secreted the patient is not subject to pernicious anaemia and treatment can usually be discontinued with safety and be replaced by careful observation.

Patients can be treated and maintained in remission on oral preparations of vitamin B_{12} and, if a sufficiently large dose is given, on this alone; or, alternatively, oral preparations can be combined with intrinsic factor, but rather disturbing reports of failure to maintain remission,[8] and of failure of intrinsic-factor preparations to promote the absorption of

orally administered vitamin B_{12}, have now appeared.[9, 10] In these cases the patients relapsed after a good initial response. This does not appear to apply to all intrinsic-factor preparations and would also appear to some extent to be species specific and probably associated with the development of antibodies to hog pyloric mucosa.[11] Other preparations containing vitamin B_{12} as a peptide complex have been stated to be efficacious,[12] but these claims have not gone unchallenged.[13, 14] Treatment with liver extract is no longer recommended—an impotent extract may be dangerous, since failure to maintain remission and even irreversible neurological change sometimes occur.[15] The best treatment for pernicious anaemia is an injection of 100 μg. of vitamin B_{12} every 3 weeks, although this dose is probably sufficient if given only once a month.[7]

1. Editorial (1959): S. Afr. Med. J., 33, 513.
2. Fudenberg, H. and Estren, S. (1958): Amer. J. Med., 25, 198.
3. Denborough, M. A., Retief, F. P. and Witts, L. J. (1958): Brit. Med. J., 1, 1213.
4. Card, W. I., Marks, I. N. and Sircus, W. (1955): J. Physiol. (Lond.), 130, 18.
5. Jacobs, A. (1958): Brit. J. Haemat., 4, 465.
6. Joske, R. A., Finckh, E. S. and Wood, I. J. (1955): Quart. J. Med., 24, 269.
7. Hemsted, E. H. and Mills, J. (1958): Lancet, 2, 1302.
8. Blackburn, E. K., Cohen, H. and Wilson, G. M. (1955): Brit. Med. J., 2, 461.
9. Stokes, J. B. and Pitney, W. R. (1958): *Ibid.*, 1, 322.
10. Lowenstein, L., Brunton, L., Shapiro, L., de Leeuw, N. and Dufresne, M. (1957): Canad. Med. Assoc. J., 77, 923.
11. Schwartz, M., Lous, P. and Meulengracht, E. (1958): Lancet, 2, 1200.
12. Heathcote, J. G. and Mooney, F. S. (1958): *Ibid.*, 1, 982.
13. Latner, A. L. (1958): *Ibid.*, 1, 1077.
14. Castle, W. B. (1958): *Ibid.*, 2, 270.
15. Adams, J. F. and Timbury, G. C. (1959): Brit. Med. J., 1, 833.

TOKSEMIE VAN SWANGERSKAP—'N VOORKOMBARE TOESTAND?

Deur al die eeue het toksemie van swangerskap die aandag van verloskundiges geniet. Eeue gelede was die ou Sjinese medisynemeesters, en ook die Griekse medici soos onder andere Hippocrates, al bewus daarvan dat 'n swanger vrou stuipe kon kry. Dit was egter nie voor die neëntiende eeu dat dit besef is dat albuminurie en 'n stygende bloeddruk aan hierdie toestand verwant is nie. Dit is ook maar eers gedurende die neëntiende eeu dat die besef posgevat het dat 'n hoë moederlike en fetale sterftesyfer hieraan toegeskryf kan word.

In die afgelope jare is baie kennis van die patologie van toksemie van swangerskap ingewin en menige behandelings is voorgestel. Wat die etiologie betref, is ons egter nog maar steeds in die duister. Die moederlike sterftesyfer in van die beste klinieke in die wêreld is gemiddeld 3·4 per 10,000 geboortes of meer as 25 persent van die alomvattende moederlike sterftesyfer van 12·5 per 10,000 geboortes. Die voorkoms van hierdie toestand in die wêreld is ongeveer 6 tot 7 persent. Dit is die algemeenste komplikasie by die jong primigravida, en die voorkoms van toksemie by die swanger vrou onder 16 jaar is drie keer so groot as by swanger vrouens oor die geheel. Dit is juis die jonger vrou wat haar vrugbare tyd nog voor het, wat aangetas word.

Moet ons dan nou maar ons hande saamvou, aangesien navorsing, wat etiologie betref, so min opgelewer het en ons behandeling so onbevredigend is? Nee, bepaald nie, want toksemie van swangerskap kan vandag beskou word as 'n voorkombare toestand.

Die Australiërs het hier die voortou geneem en in 1952 het Hamlin[1] sy werk oor die belangrikheid van gewigstoename in swangerskap gepubliseer. Die gevolg hiervan was dat die voorkoms van toksemie van swangerskap in Australië geweldig afgeneem het en dat eklampsie 'n amper onbekende toestand in daardie land geword het. Ander lande het gevolg en baie bevredigende rapporte bereik ons nou van oor die hele wêreld.

Wat van Suid-Afrika? Helaas, in ons land waar ons op alle gebiede met die wêreld probeer meeding en waar ons in baie vertakkings van die medisyne net so ver gevorder het as die meeste van die vooraanstaande lande, moet ons met geboë hoofde erken dat eklampsie nog steeds hier baie slagoffers eis en dat die voorkoms van toksemie van swangerskap nog so hoog as 15 tot 18 persent is. Waar lê die fout dan?

In 1956 het Hughes[2] die redes vir die sukses in Australië onder die volgende drie hoofde saamgevat: (1) Opvoeding van die pasiënte, (2) strenge beheer oor voorgeboortelike besoeke, en (3) vermeerdering van die beskikbare beddens vir voorgeboortelike gevalle in die hospitale. Bestee ons genoeg tyd aan ons kraam pasiënte en verduidelik ons aan hulle die belangrikheid van gereelde voorgeboortelike ondersoeke? Die meet van die bloeddruk, die betasting van die buik, en die toets van die urine is nie al waaruit 'n voorgeboortelike ondersoek bestaan nie. Die nege maande van swangerskap en die verwagte bevalling daarna is vir die meeste vrouens iets onbekend. Vrees kan dus baie maklik deur stories van vorige moeders en artikels in tydskrifte by hulle ingeboesem word. Die vrou se vertroue moet gewen word en daar moet nadruk gelê word op die feit dat baie latere komplikasies deur getroue nakoming van voorgeboortelike sorg en ondersoeke verhoed kan word. Hierdie optrede moet nie aan die ontspanningsklasse oorgelaat word nie, maar moet deur die persoon wat die bevalling gaan waarneem self onderneem word. In normale gevalle behoort voorgeboortelike ondersoeke tot 30 weke elke 4 weke, en vanaf 30 tot 36 weke elke 2 weke, en daarna weekliks, gedoen te word. Indien iets abnormaals gevind word, behoort die ondersoeke meer dikwels te wees. Daar moet streng daarop gelet word dat die pasiënte gereeld kom. Daar word vertel dat pasiënte in Australië deur ambulanse gehaal word as hulle nie hul voorgeboortelike afsprake gereeld nakom nie.

In meeste van ons hospitale is daar so min kraambeddens beskikbaar dat 'n pasiënt alleen toegelaat word as sy op die punt staan om eklampsie te ontwikkel. Die minimum vereistes wat vir 'n kraamafdeling gestel word, is dat ten minste 20 persent van die beddens vir voorgeboortelike gevalle beskikbaar behoort te wees. In ons land is kraambeddens in die meeste van ons hospitale afgeskeep. Ons as medici het ook hieraan skuld, want ons het nog nie aan die staat genoegsame bewyse gelewer dat hierdie beddens essensieel is nie. Kan van ons groter hospitale dan nie meer beddens vir hierdie gevalle beskikbaar stel nie—al moet hulle ook minder gevalle bespreek vir bevalling in die hospitaal? Alleen op hierdie manier kan die nodige gegewens ingewin en die bewyse gelewer word.

Toksemie van swangerskap is 'n voorkombare toestand en ons as medici het 'n deel van die antwoord gevind. Ons is dit aan ons nageslag verskuldig om te sorg dat die toestand sover moontlik voorkom word. Dan sal ons nie deur die res van die wêreld in die skadu gestel word nie. Elders in hierdie uitgawe publiseer ons 'n artikel oor *The Management of the Toxaemias of Early Pregnancy* waarin aspekte van die breëre probleem van toksemie behandel word.

1. Hamlin, R. H. T. (1952): Lancet, 1, 64.
2. Hughes, T. D. (1956): Med. J. Aust., 2, 48.