ANEMIAS IN NEPAL

William H. Adams M. D.*

Several studies describing the presence or absence of abnormal hemoglobins and beta thalassemia among the Nepalese have been reported. The varieties of disorders have included hemoglobin H disease, beta thalassemia, and hemoglobin E (Brain and Vella, 1959; Weatherall and Vella, 1960; Vella, 1962; Chatterjea, 1959). However, only one survey for such abnormalities which has taken place in Nepal itself has been published, that being among the Sherpas, where one case of beta thalassemia was found among 129 subjects examined (Jackson, Lehrmann and Shariah, 1960). During the past year, a survey has been carried out by the Johns Hopkins University International Center for Medical Research and Training, in cooperation with H. M. G. Directorate of Health Services, to define these areas in Nepal where genetic hemoglobin abnormalities pose a significant medical problem. In addition data was obtained regarding certain acquired anemias.

The study of congenital anemias has involved hemoglobin electrophoresis on over 1900 persons from various areas of Nepal. Of the more common hemoglobinopathies, three can be promptly dealt with. Hemoglobin C and Hemoglobin S have not been found in this survey. This does not mean their non-existence in Nepal. Considering the high frequency of sickle hemoglobin in certain tribes in India, it seems unlikely that there would be no Hemoglobin S in Nepal. But data so far obtained do not suggest appreciable clinical problems caused by sickle hemoglobin in any of the areas surveyed. Hemoglobin D, found in approximately 2% of people in Punjab of North India, has only occasionally been found in Nepal. Therefore we turn to what so far appears to be the main hemoglobinopathy, Hemoglobin E. Figure 1 shows the prevalence of Hemoglobin E in the areas surveyed. Note that the highest prevalence, 4%, was found in Southeast Nepal. The Hemoglobin E heterozygote is considered clinically hematologically normal, as is the general case with the Hemoglobin S heterozygote. However, in contrast to the sickle hemoglobin, a person with Hemoglobin E disease has only a mild anemia and is not prone to the painful crises seen with sickle cell anemia. Therefore Hemoglobin E is not a very important clinical problem except that it may be confused with

* The Johns Hopkins University International Center for Medical Research and Training.
iron deficiency. Interest then centers on why Hemoglobin E exists at all. It is well documented that Southeast Asia is the reservoir of populations with an extremely high prevalence of Hemoglobin E, sometimes approaching 50% (Wasi et al, 1969; Aung-Thu-Batu et al, 1971; Couffon and Du Sassy, 1969). It is associated with the more primitive Indo-Mongoloid populations, and is not often found among modern Chinese (Lehmann and Hunstman, 1968). It appears from the distribution of Hemoglobin E in Nepal that we are seeing the fringe of this Southeast Asian Hemoglobin E focus. This is identical to the situation in India, where Hemoglobin E is found in about 4% of Bengalese, but is uncommon further west. Thus, the Nepal data adds one more bit of information that suggests that there is a selective genetic process at work that perpetuates Hemoglobin E in Southeast Asia and that this is rapidly lost peripherally. What the selective process is unknown. It does not appear to be malaria or iron deficiency.

The second congenital anemia studied has been thalassemia. It has been said that wherever one bothers to look for thalassemia, it will be found. And so it has been the case in Nepal. Because of difficulties inherent in diagnosing thalassemias, accurate prevalence figures cannot be given except for two populations; approximately 60 subjects from the high-altitude village of Langtang and 151 unselected admissions to the maternity service, Bir Hospital, in Kathmandu. The prevalence was 0 and 4% respectively. Despite data limitations including limited selective screening of hypochromic anemias at the Bir Hospital, it seems reasonable to suggest one point, that being that thalassemia may be more common in Nepal that abnormal hemoglobins. The % of thalassemics among 350 subjects studied was 7% but, of over 1900 specimens electrophoresed, the overall incidence of abnormal hemoglobins was only 1.2%. Although beta thalassemia major and minor, beta thalassemia-Hemoglobin E disease, alpha thalassemia minor, and Hemoglobin H disease have been identified during the past year's studies, data are too limited to give any idea of ethnic distribution.

With regard to acquired anemias, I am speaking of nutritional and blood loss anemias. Serum iron levels, one of the accepted bases for defining iron deficiency, were unavailable. Therefore, on the basis of hypochromia, either as defined by a low mean corpuscular hemoglobin concentration (MCHC) or by anemia and a hypochromic peripheral smear, the following observations were made. In Udaipur district of South Nepal, altitude near sea level, 50% of 190 subjects examined had low MCHCs. In Kathmandu, altitude 4000 feet, 20% of 151 pregnant women studied at Bir Hospital had low MCHCs. In Jumla, West Nepal, altitude 7,500 feet, 12% of 60 subjects had a hemoglobins below what one would expect at that altitude. In Langtang, North Nepal, altitude 11,500 feet, only 7% of 58 subjects had low MCHCs. Most subjects examined in the three areas outside Kathmandu were males. Thus, although the evidence is indirect, there appears to be a marked decrease in the incidence of iron deficiency, and this implies blood loss, as one goes from low to high altitude in Nepal. How much hookworm infestation or other factors are involved in this decline is unknown.
Prolate deficiency was looked for in the high altitude village of Langtang. The diet of persons living at high altitude seemed notably lacking in green vegetables, although this is without doubt seasonal. Red cell folate levels were performed on 45 subjects, mostly adults. Specimens were collected in October, after two harvest seasons. There were 6 subjects with red cell folates that ranged between 116 to 150 nanograms per ml, a borderline range. All others were higher. However, all of 52 subjects had normal serum folates, the lowest being 5.2 nanograms per ml. Thus, at least during harvest time, significant folate deficiency was not found in Langtang. In addition, the folate content of yak milk, an important part of their diet, was found to be approximately 60% of that found in human fresh cow's milk. However, as the milk is routinely boiled, this will decrease the folate content even further. The vitamin B12 content was equal to that of cow's milk.

Another study, done in collaboration with Dr. Gurung, Chief of the Obstetric and Gynecology Section, Bir Hospital, involved a survey of 151 unselected, but for the most part consecutive, admissions to the maternity service (Gurung and Adams, 1972). If the lower limit of normal hemoglobin for pregnant women is adjusted for the altitude of Kathmandu, being 4,000 feet, data of others suggest that anemia for these subjects should be defined as hemoglobins less than 11.5 gm%. If one accepts this definition, then 1/3 were anemic, but most only to a mild degree. Of subjects with hemoglobin below 9 gm%, all had hypochromia. Thus iron deficiency and to a small degree thalassemia appeared to be the primary causes of the more severe anemias of pregnancy seen in this study. Serum B12, red cell and serum folate determinations were performed on all anemic and some normal subjects. Folate levels revealed only one subject to have an unequivocally low serum and red cell folate. Her hemoglobin was 9.1 grams% and the anemia was normochromic. A comparison of serum and red cell folates between non-anemic and normochromic anemic subjects showed no significant difference. However, serum B12 determinations indicated 9 women had levels between 68 and 112 picograms per ml, which are in the deficiency range with the Euglena assay used. Therefore one may say that in this population iron deficiency and to some extent thalassemia produces the greatest number and most severe maternal anemias. Evidence for significant folate deficiency was very uncommon. This also indicates the low B12 levels were not a consequence of folate deficiency. As serum B12 tends to decrease as pregnancy progresses, it cannot state definitely that the low B12 levels in fact indicated depletion of maternal B12 stores. However, indirect evidence that this was true nutritional B12 deficiency is indicated by the observation that, of 23 hematologically normal controls, only one had a low value; of 23 women with hypochromic anemia, again only one had a low B12 value; but of 25 subjects with normochromic anemia, 7 had low serum B12. Thus these data unexpectedly suggest that nutritional B12 deficiency rather than folate deficiency is a significant cause of macrocytic anemia of pregnancy in Kathmandu.

The hematology of the new born was included in the maternity study. And, pertinent
to Nepal, studies in other high altitude areas suggest that the human newborn is hematologically adapted to sea level, no matter at what altitude he is born. During the maternity study of the past year, paired maternal and newborn data were obtained on 122 delivers. The average hemoglobin of the mothers was 11.7gm%, of newborns, 16.5gm%, and the mean birth weight was 6.3 lbs. Nepali newborn hemoglobin levels were virtually identical to those found in studies in the United States. Thus the accepted definition for anemia of the newborn in the United States, being 14gm%, applies to Nepal also. There was no correlation between maternal and newborn hemoglobin levels. However there was a positive correlation, significant at the 2% levels between maternal hemoglobin and birth weight. As weight is directly proportional to blood volume, this indirectly suggests an intimate association between maternal anemia and the newborn red cell mass as well as birth weight.

Now I wish to discuss data pertaining to high altitude. One important adaptive mechanism to altitude is an increase in the rate of erythropoiesis and consequently an increase in red cell mass. Assuming a constant plasma volume, hemoglobin levels will obviously increase. Of interest here is the observation that apparently normal males from Langtang village, altitude 11,500 feet, had much lower hemoglobins than those expected from numerous studies of other populations living at similar altitude anywhere in the world (Hurtado et al, 1945). Likewise, Langtang females and also Tibetan males residing in a nearby camp, altitude 10,500 feet, were significantly lower than Langtang males. Thus sampling bias does not seem to be the cause of this phenomenon. All subjects had normal MCHCs, A2 and fetal hemoglobin levels, and the mobility of the major hemoglobin component was the same as the normal hemoglobin A. Whether these lower hemoglobin values of persons of Tibetan descent, if confirmed, represent a genetic difference in control of erythropoiesis, a more efficient mechanism involved in oxygen transport, or a different balance between red cell mass and plasma volume should be the basis for future study. It may be that the definition of anemia requires alteration for certain ethnic groups, although previous studies have not suggested this.

Figure 1: Regional distribution of Hemoglobin E in Nepal.
Bibliography