# Pernicious Anemia in Southwestern American Indians

By Maurice L. Sievers, Allan L. Metzger, Leonard S. Goldberg, and H. Hugh Fudenberg

Pernicious anemia (PA), previously considered rare among American Indians, was diagnosed in 18 Indians during a 16-yr period at the Phoenix Indian Medical Center. These patients, from ten different tribes, did not vary significantly from all adult hospital admissions in proportionate sex, tribe, or blood group distribution. The current minimum prevalence of PA for southwestern Indians is 1:514 beyond 50 yr of age and 1:293 after 60 yr of age. Despite a marked predominance of blood group 0 (81%), the Indians developed PA as frequently as other ethnic groups in which PA is strongly associated with blood group A. Their clinical and hematologic manifestations were similar to those of whites with PA. Of the 13 subjects tested immunologically, 11 demonstrated parietal cell antibodies, and six had blocking antibodies to intrinsic factor. During follow-up none developed gastric carcinoma, although this tumor—the most frequent malignancy among southwestern Indians—is correlated with PA in whites. The findings establish that PA in full-blooded southwestern Indians is not rare and is clinically and immunologically similar to PA in whites.

PERNICIOUS ANEMIA (PA) is characterized in current medical textbooks[1,2] as occurring predominantly in whites living in the temperate zone of North America and Europe. Only a few case reports of American Indians with PA have been published.[3-6] The purpose of this paper is to establish that, in fact, PA is not infrequent among southwestern American Indians. This report presents prevalence data for PA in Indians, which are largely unavailable for other ethnic groups. The clinical, laboratory, and immunologic findings of the disease in this population are also described.

## MATERIALS AND METHODS

All cases of established PA in American Indians who were treated at the Phoenix Indian Medical Center (PIMC) between July 1, 1955 and June 30, 1971 are included in this report. During these 16 yr, the PIMC had 38,982 hospital admissions and 426,130

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outpatient visits. Since this hospital is the referral center for more than 55,000 southwestern Indians from Arizona, California, Nevada, and Utah, as well as the primary medical facility for the Indians of nearby reservations and communities, it was possible to determine the minimal prevalence of PA in a well-defined population.

Each diagnosis of PA was made during hospitalization and was reconfirmed by retrospective chart review. Diagnostic criteria included: macrocytic anemia; megaloblastic bone marrow, histamine- or betazole-fast achlorhydria, laboratory evidence of cyanocobalamin ($B_{12}$) and intrinsic factor (IF) deficiency (either two-part Schilling test, with and without IF, or depressed serum $B_{12}$ level), and brisk reticulocytosis following intramuscular administration of small doses (0.5–2 $\mu$g) of $B_{12}$.

Follow-up studies in August 1971 among the 14 living patients included a detailed history and physical examination, completion of any appropriate tests previously omitted (gastric analysis, Schilling test, and blood typing); upper gastrointestinal x-ray examination, and determinations of hematologic status, plasma glucose (fasting and 2 hr after 75 g Glucola), blood urea nitrogen, thyroid function tests (serum $T_3$, $T_4$, $T_7$), and serum calcium and inorganic phosphorus. In addition, serum immunoglobulin levels were measured by radial immunodiffusion.[7] Antibodies to gastric parietal cells (GPC), thyroid microsomal antigen, and adrenal tissue were determined using indirect immunofluorescent techniques.[8] Blocking antibody to IF was measured by a charcoal assay,[9] and binding antibody to the IF-$B_{12}$ complex was measured by radioimmunodiffusion.[10]

## RESULTS

During the 16 yr of observation, 18 Indians with PA were evaluated at the PIMC. The average case finding rate of 1.1/yr was stable and showed no significant trend by 4-yr intervals. The tribal distribution of the patients with PA is compared with that for all adult PIMC admissions in Table 1. There are no significant differences in the composition of the two groups. Over-all, PA occurred among ten tribes.

### *Clinical and Laboratory*

All of the 18 Indian patients with PA presented with weakness or fatigue. Their proportion of ten women (56%) and eight men (44%) approximates the over-all adult PIMC admission distribution of females (53%) and males (47%). The mean age at the time of diagnosis was 66.3 yr (range 51–91 yr). None of them had vitiligo or premature graying of the hair, conditions reported to be associated with PA in whites.[1,11]

Table 1. Comparison of Tribal Distribution Between Indian Patients With Pernicious Anemia and All PIMC Adult Admissions, 1955–1971

| Tribe | PIMC Adult Admissions (%) | PA Patients % | PA Patients No. |
|---|---|---|---|
| Pima | 31 | 39 | (7) |
| Apache | 21 | 17 | (3) |
| Papago | 12 | 6 | (1) |
| Navaho | 10 | 6 | (1) |
| Hopi | 5 | 6 | (1) |
| Other southwestern tribes | 17 | 22 | (4)* |
| Nonsouthwestern tribes | 4 | 6 | (1)† |

*Hualapai, Yavapai, Havasupai, Yaqui-Papago.
†Chickasaw-white.

Of the 16 in whom blood types were determined, 13 (81%) were group O, and the other three (19%) were group A; all were Rh positive. These findings conform to the observed blood type distribution (80% group O, 20% group A, and 100% Rh positive) of southwestern Indians with the proportionate tribal representation of the patients with PA.[12,13]

Achlorhydria refractory to histamine or betazole was demonstrated in all 18 patients. The peripheral blood smears of all 18 Indians with PA revealed macrocytic erythrocytes, and morphologic examination of bone marrow in 14 of the subjects demonstrated the characteristic megaloblastic changes of PA.[14] Pancytopenia occurred in 63% (10 of 16) of the cases evaluated. Additional pertinent laboratory findings for the 18 Indian patients with PA are shown in Table 2.

Baseline Schilling tests without IF in 12 patients revealed subnormal (7% or less) radioactive $B_{12}$ excretion in all except one subject who had a borderline result (7.5%) but had both blocking and binding IF serum antibodies. Ten of these 12 patients had second-stage Schilling tests with administration of IF; in eight the results substantiated the diagnosis of PA, with radioactive $B_{12}$ excretion increasing to greater than 7%. In the remaining two, the change in urinary $B_{12}$ excretion with IF was below the diagnostic level, although the increase in $B_{12}$ excretion with IF was at least threefold (0.7%–4.8%, 2.1%–6.2%). Furthermore, both patients had GPC antibodies, and one had blocking antibodies against IF. No other etiology (malabsorption, "blind loop syndrome," or chronic alcoholism with gastritis) for this $B_{12}$ deficiency-type macrocytic anemia was detected. Therefore, since these two patients fulfilled the major diagnostic criteria for PA, the nondiagnostic but, nevertheless, significant increases in $B_{12}$ excretion with IF administration strongly support the diagnosis. Five of the six subjects in whom Schilling tests were not done received parenteral therapeutic test doses of $B_{12}$ (0.5–2 $\mu$g) as did ten of the others. All 15 of these patients demonstrated prompt reticulocytosis with peak levels attained between the fifth and eighth days.

Because of the reported increased frequency of several endocrine disorders in whites with PA,[15] the Indians with PA were evaluated for diabetes mellitus and thyroid and parathyroid disease. Diabetes mellitus[16] was diagnosed in seven of the 18 patients. This frequency approximates the general rate expected for southwestern Indians with this age, sex, and tribal distribution.[13,17] There was no clinical or laboratory evidence of either thyroid or parathyroid disease.

*Immunologic Studies*

Fasting blood samples from 13 of the surviving Indian patients with PA were examined for antibodies against GPC, IF, thyroid microsomal antigen, and adrenal tissue, as well as for serum immunoglobulin (Ig) levels (Table 3). These findings were compared with six Indian controls without PA (matched for tribe, age, sex, and diabetes mellitus), and 19 age- and sex-matched whites with PA. GPC antibodies were detected in 11 of 13 Indians with PA, in one of six Indian controls, and in 17 of 19 whites with PA.

Table 2. Individual Findings at Time of Diagnosis of Pernicious Anemia in 18 Indians

| Patient | Age, Sex | Bl Gr* | Hb | Hct | Ret | WBC | P/L | Plt | Meg Mar | Achl GA | Retic With $B_{12}$ | LDH | Bili | Schilling Test: Without IF | Schilling Test: With IF | Hct p $B_{12}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| R.A.S. | 51 F | O+ | 4.1 | 14 | 1.1 | — | — | — | + | + | 16.7 | — | 0.9 | 0.7 | 4.8 | 39 |
| R.S. | 72 M | O+ | 5.0 | 12 | 0.6 | 4000 | 48/52 | 70,000 | + | + | 9.1 | — | 0.7 | 1.6 | 10.9 | 40 |
| M.C. | 58 F | O+ | 3.0 | 9 | 0.8 | 2150 | 47/47 | 42,000 | + | + | 30.0 | — | — | 7.5 | — | 35 |
| F.D. | 70 F | O+ | 6.1 | 17 | 0.1 | 3750 | 44/54 | 140,000 | + | + | 11.9 | — | 1.1 | 1.6 | 7.9 | 43 |
| N.M. | 56 F | O+ | 4.7 | 15 | 0.5 | 6900 | 67/33 | — | + | + | 18.9Ψ | >10,000 | 1.7 | 0.8 | 11.0 | 36 |
| E.J. | 63 F | O+ | 6.8 | 23 | 0.4 | 3150 | 32/59 | 72,000 | + | + | 18.5 | — | 1.0 | 2.5 | 10.7 | 36 |
| M.H. | 80 M | O+ | 3.7 | 14 | 0.2 | 3750 | 84/15 | 68,000 | + | + | 8.0 | 1,040 | 1.9 | 2.0 | 9.0 | 39 |
| E.P. | 57 F | O+ | 5.2 | 16 | 0.3 | 2100 | 27/73 | 152,000 | + | + | 7.3 | 1,970 | 2.8 | — | — | 44 |
| A.E. | 59 F | A+ | 8.7 | 27 | 0.9 | 3690 | 45/45 | 133,000 | + | + | 16.6 | 500 | 1.5 | 2.0 | 13.0 | 43 |
| R.A. | 91 F | O+ | 5.1 | 15 | 0.3 | 4420 | 34/49 | 92,000 | + | + | 12.4Ψ | — | 1.8 | 2.0 | 16.0† | 37 |
| E.W. | 75 F | O+ | 4.7 | 15 | 0.1 | 2400 | 43/53 | 10,350 | — | + | 15.0 | >2,000 | 1.1 | 2.1 | 6.2 | 36 |
| J.F. | 54 M | A+ | 7.1 | 22 | 1.5 | 4600 | 68/24 | 71,000 | — | + | 16.5 | 3,240 | — | 1.5 | 9.0 | 43 |
| J.P. | 56 M | O+ | 6.3 | 16 | 1.7 | 3000 | 67/29 | 180,000 | + | + | 28.3 | — | 0.9 | — | — | 43 |
| L.S. | 60 M | O+ | 4.8 | 13 | 0.3 | 2800 | 28/68 | 90,000 | — | + | 14.8 | — | 2.0 | — | — | 39 |
| K.Mc. | 74 F | A+ | 5.2 | 17 | 0.2 | 1900 | 18/79 | 80,000 | + | + | 11.5Ψ | — | 1.7 | — | — | 42 |
| J.S. | 63 M | — | 5.6 | 18 | 0.1 | 3100 | 78/24 | 46,000 | + | + | 10.0 | >2,000 | 1.8 | 2.0 | — | 38 |
| R.E.T. | 81 M | — | 7.0 | 19 | 1.1 | 5000 | 58/38 | 251,000 | — | + | 9.5 | — | 1.8 | — | — | 40 |
| R.T. | 73 M | O+ | 3.6 | 7 | 1.0 | 2100 | 36/63 | 185,000 | + | + | 11.5 | — | 3.4 | — | — | 43 |

*Abreviations and units: Bl Gr, blood group, ABO and Rh types; Hb, hemoglobin (g/100 ml); Hct, hematocrit (%); Ret, reticulocytes (%); WBC, white blood count/cu mm; P/, polymorphonuclears/lymphocytes (%); Plt, platelets/cu mm; Meg Mar, megaloblastic bone marrow; Achl Ga, histamine- or histalog-fast achlorhydria on gastric analysis; Retic with $B_{12}$, reticulocytes 5–8 days after 0.5–2 μg cyanocobalamin ($B_{12}$) intramuscularly (results followed by Ψ=>2 μg $B_{12}$); LDH, serum lactic dehydrogenase (U/ml); Bili, serum bilirubin (mg/ml); Hct p $B_{12}$, hematocrit 4–6 wk after $B_{12}$ therapy; IF, intrinsic factor (%); +, present; —, test not done.

†Serum $B_{12}$ level for RA also subnormal (<50 pg/ml).

Table 3. Current Laboratory and Serologic Findings in 13 Indian Patients with Pernicious Anemia

| Patient | Age and Sex | Follow-up (yr) | Serum Antibodies | | | Serum Immunoglobulins (mg/ml) | | |
|---|---|---|---|---|---|---|---|---|
| | | | | IF (titer) | | | | |
| | | | GPC* | Blocking | Binding | IgG | IgA | IgM |
| R.A.S. | 66 F | 15 | + | +(3550) | +(4) | 11.50 | 3.40 | 0.38 |
| R.S. | 84 M | 12 | + | − | − | 27.00 | 4.50 | 0.80 |
| M.C. | 68 F | 10 | − | +(8530) | +(8) | 17.50 | 4.50 | 1.10 |
| F.D. | 77 F | 7 | + | +(9530) | − | 17.50 | 2.50 | 0.87 |
| N.M. | 62 F | 6 | + | +(2560) | − | 20.00 | 3.20 | 1.35 |
| E.J. | 68 F | 5 | + | − | − | 17.50 | 2.10 | 1.05 |
| M.H. | 85 M | 5 | + | − | − | 17.50 | 4.00 | 0.87 |
| E.P. | 61 F | 4 | − | +(8350) | − | 17.50 | 0.84 | 0.87 |
| A.E. | 61 F | 2 | + | − | − | 17.50 | 6.00 | 1.05 |
| R.A. | 92 F | 1 | + | − | − | 15.00 | 1.80 | 1.15 |
| E.W. | 76 F | 1/2 | + | − | − | 20.00 | 4.50 | 1.10 |
| J.F. | 54 M | 1/3 | + | − | − | 20.00 | 4.30 | 1.60 |
| J.P. | 61 M | 5 | + | +(2530) | − | 10.00 | 6.00 | 1.05 |

*GPC, gastric parietal cell; IF, intrinsic factor; Ig, immunologlobulin; +, test result positive; −, test result negative.

Blocking antibodies to IF were found in 6 of 13 sera of Indians with PA, in none of six Indian controls, and in 12 of 19 sera from whites with PA. Both blocking and binding antibodies to IF were present in the sera of two of the Indians and in three of the white patients with PA. IF blocking antibodies were noted in the sera from the only two Indians with PA in which GPC antibodies were not demonstrated; one of these sera also contained IF binding antibodies. Nine of the 11 Indians with GPC antibodies had blood group O, and the other two had blood group A. Thyroid antibodies were demonstrated in one of the 13 Indian patients with PA (MH), in one of the six Indian controls, and in one of the 19 whites with PA. None of the patients in these three groups exhibited adrenal antibodies.

The mean levels of serum immunoglobulins (mg/ml) for the Indian patients with PA, the Indian controls, and white patients with PA were, respectively: IgG—18.35, 19.92, and 12.65; IgA—3.66, 4.92, and 1.63; and IgM—1.02, 1.05, and 1.50. No significant difference between the Indian patients with PA and matched Indian controls was noted; however, in comparison with mean serum IgG and IgA levels in the white patients with PA, the Indians' values were significantly elevated (IgG, $p < 0.01$; IgA, $p < 0.001$). Serum IgM levels for all three groups were similar.

*Follow-up*

Four of the 18 Indian patients with PA died of causes unrelated to PA. The mean follow-up period for survivors was 6 yr (range, 4 mo–15 yr). Despite their advanced ages, they are currently in good health. All have received regular monthly parenteral $B_{12}$ therapy, as substantiated by chart review and normal current hematologic findings. Gastric carcinoma has not been detected, either by radiographic examination in the 14 survivors or by necropsy in two of the four who have died.

## DISCUSSION

The premise in current textbooks of medicine[1,2] and hematology[14] that PA is principally a disease of inhabitants of the European and North American temperate zone (particularly the Scandinavian, English, and Irish) requires some modification. Its occurrence has been documented in people from other areas—the Asiatics,[18] African,[19,20] and American blacks.[21–23] Since 1960, isolated reports of ten American Indians with PA have been published.[3–6] One of these Indians had the juvenile onset type of disease,[5] while all of the others were adults; these cases fulfilled most of the major diagnostic criteria for PA. In the present investigation, the characteristics of PA in 18 American Indians have been critically evaluated. There were ten different tribes (Arapaho, Cherokee, Cheyenne, Chippewa, Choctaw, Creek, Gros Ventre, Nez Percé, Potawatomi, and Sioux) among the previously published cases, nine of which were full-blooded Indians. In this study, 17 of the 18 Indians with PA were full-blooded, and their ten tribes all differ from those of the earlier reports. Thus, PA has been documented among at least 20 American Indian tribes of diverse geographic and genetic origin.

There are insufficient data to determine the exact frequency of PA in most white, black, and Indian groups, not only because of the variable underdiagnosis of the disease, but also because of uncertainty regarding population characteristics. During this investigation the rate for the diagnosis of PA averaged 1 case per 817 hospital medical admissions. Reported hospital admission prevalence rates for PA in American whites are 1:660–1:1086 and in American blacks, 1:1240–1:1515.[21,22] Precise interpretation of these comparative frequencies is impossible because of repetitive individual admissions of an indeterminate extent, selectivity of the hospital population, and the lack of age adjustment of data.

The current prevalence of known PA among these southwestern Indians is 1:3929, or for those over 50 yr of age (7200), 1:514. These rates may slightly underestimate the true frequency because PA might be diagnosed and treated for a small number of the Indians at reservation facilities and, therefore, not be referred to the PIMC. Random population samples were surveyed in three different regions of Great Britain for the prevalence of anemia and for serum $B_{12}$ levels.[24–26] Among subjects aged 65 yr and older, PA was discovered in 1 of 271 individuals from one region[24] and in none of 533 persons from another area.[25] These findings compare with the prevalence of PA in the Indians of 1:298 for this same age group (9 cases among 2679 Indians) and 1:293 (13 of 3814) for those 60 yr and older. The average minimal yearly incidence of newly diagnosed PA (1.1 case/yr) in 50-yr and older southwestern Indians is 15/100,000.

The characteristics of PA in Indians—age at diagnosis, sex ratio, insidiousness of onset, hematologic findings, elevated serum gastrin,* and refractory achlorhydria—are indistinguishable from those in whites.[1,2,14] Furthermore, the gastric mucosa of the only autopsied Indian with PA (RT) whose stomach was examined microscopically revealed the typical histologic findings of chronic atrophic gastritis that are found in whites with this disease.[14] Although an increased frequency of diabetes mellitus and thyroid and parathyroid disease has been reported for whites with PA,[15,29] these associations were not found in southwestern Indians. As expected PA occurred late in life, with 8 of the 18 Indian patients more than 70 yr old at the time of diagnosis. Nevertheless, survival with treatment has been excellent, ten having lived more than 5 yr and four more than 10 yr.

White patients with PA have an increased frequency of blood group A.[29,30] In contrast, the Indians with PA have the same marked predominance of blood group O, as the general southwestern Indian population.[12,13] Despite this greater proportion of blood group O in Indians, the prevalence of PA apparently does not differ significantly in the two races. Gastric carcinoma

*A significant ($p < 0.001$) increase of the serum gastrin levels for 13 Indian patients with PA (355 ± 272 pg/ml) in comparison with 20 Indian controls (57 ± 29 pg/ml), as measured by radioimmunoassay[27] in the laboratory of Dr. Bernard Jaffe, Department of Surgery, Washington University School of Medicine, St. Louis, Mo., is consistent with reported observations for non-indians with PA[28].

was not observed in the present series of patients with PA, although this malignancy is the most frequent one in southwestern Indians, and achlorhydria is more common than in whites of the same age and sex.[16] However, Indians with gastric carcinoma do not have the excess of blood group A (Sievers, M. L., unpublished data, 1972) that has been noted among whites and blacks with this malignancy.[29,30] It would be significant if any characteristics of PA differed between those with blood group O and those with group A. In this study no such dissimilarity was found.

Since autoimmune phenomena may be involved in the etiology and/or perpetuation of PA in whites, various immunologic studies were done in the Indian patients. As has been noted for whites,[31] the Indians exhibited GPC antibodies significantly more often with than without PA. The frequencies of GPC antibodies (85%) and IF antibodies (46%) in the Indians with PA approximate the rates reported among whites with PA.[29,32] However, the detection of IF antibodies in two Indians with PA who lacked GPC antibodies contrasts with reports that whites rarely demonstrate IF antibodies in the absence of GPC antibodies.[32] The presence of thyroid cytoplasmic autoantibodies in only one Indian and one white patient with PA is unusual, since this antibody reportedly occurs in 30%–50% of whites with PA.[32,33] Compared with whites, southwestern Indians (both with and without PA) demonstrated elevated serum levels of IgG and IgA, a finding not reported previously and possibly due to prolonged immunologic stimulation from chronic exposure to infections.

It is apparent that Indians and whites with PA are remarkably similar in their clinical, hematologic, and immunologic disease characteristics. Furthermore, the prevalence data of this study establish that PA is not rare among full-blooded southwestern Indians. Indeed, the Indians, having predominantly blood group O, develop PA as frequently as other races in which PA is correlated with blood group A. Therefore, clinicians should give PA as much diagnostic considerations in American Indians as in other ethnic groups.

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