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Staff Meeting Report

The Diagnostic Use of Radioactive Chromium in Hemolytic Anemias*†

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"The essential feature of a hemolytic anemia is a reduction of the life span of the patients' erythrocytes." With this opening sentence, Dr. J. V. Dacie begins his excellent monograph, *The Hemolytic Anemias.*[1] The meaning of this is clarified when one considers that all other hematological studies in hemolytic anemias with the exception of the erythrocyte life-span are but indirect measurements of the dynamics present. The equilibrium that is maintained between destruction and production is reflected in diverse manners. The hemoglobin concentration in compensated hemolytic processes may be normal and stable; yet increased rate of destruction and, therefore, decreased life-span of the erythrocytes are present. Increasing reticulocytosis signifies active erythroid regeneration; but impairment of marrow synthesis may not allow reticulocyte development as excess hemolysis continues. Bilirubinemia may be a result of impairment of clearance and may not be correlated with rate of red cell destruction at all. Fecal urobilinogen, the most accurate of all the indirect methods, is subject to scrutiny from both practical and theoretical considerations. Therefore, there arises a clinical need for a more direct method of analysis of the dynamic state of erythrocyte life span.

The observation by Gray and Sterling[2] in 1950 that radioactive chromium is bound to the red cell has subsequently provided an extremely useful adjunct in the study of hemolytic anemias. Radioactive chromium labelled red cells have served admirably as a tool by which erythrocyte life span may be measured in known clinical conditions[3, 4, 5]. Alterations of the red cell survival *in vivo* as determined by this method have been utilized by the authors as a diagnostic aid in auto- and cross-transfusion studies in delineating extracorpuscular or

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* This is a report given at the Staff Meeting of the University of Minnesota Hospitals on March 29, 1957.

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intracorpuscular defects and in documenting the effects of therapy. Because of the general interest in this technique, the physiology and basic mechanisms of the radioactive chromium red cell survival studies will be outlined. The specific benefits obtained from this method in patients seen on our pediatric service will be presented in case study material.

Physiology of the Chromium Red Cell Survival

Gray and Sterling[2] in their original description noted that the globin portion of red cells retained 97 per cent of the radioactivity attributable to the chromium tag. The cell membrane contained 1-2 per cent of the activity which was due to the absorption of globin on the membrane. The mechanism of the tagging is probably best explained as a physico-chemical linkage. This concept is supported by the observation that the hexavalent chromium ion in $Na_2\ CrO_3$ will label the red cell whereas in the trivalent form, as in $CrCl_3$, a useful label is not provided.

Ebaugh *et al*[6] determined that the chromium ion after once labelling the red cell is not re-utilized in the body. In these studies the investigators hemolyzed previously tagged red cells and then added new red cells to the hemolysate. No uptake of the chromium by the added red cells was noted. We have repeated these studies and in like manner find no evidence of "retagging" of new red cells by chromium released from previously tagged cells.

Read[7] was able to demonstrate that the addition of ascorbic acid after tagging prevented the excess $Na_2\ CrO_3$f in the system from entering the red cell. This phenomenon is best explained on the basis of a reduction of the hexavalent chromium to the trivalent form.

The normal red blood cell survival curve in adults was then obtained by use of the $Na_2\ CrO_3$. The chromium "*apparent*" red cell half life ($T\frac{1}{2}$) was noted to be only 28-30 days. In our own hands, a normal half time survival of red blood cells tagged with chromium ranges from 24-30 days. This of course differs from and is not consistent with the known red cell life span of 120 days. Ashby's[8] technique, in the hands of numerous investigators [9, 10, 11] using differential agglutination, demonstrated that 120 days is the approximate life survival of the erythrocyte. Shemin and Rittenberg[12] had arrived at a similar conclusion by feeding N^{15} glycine. This isotope was incorporated within the heme portion of the red cell. Measurement for survival of N^{15}

as atoms per cent excess in heme was observed. The average survival of the heme N^{15} was noted to be 127 days. Excellent confirmation of this figure has been obtained from C^{14} experiments done in similar manner.[13]

The apparent red cell half life of the Cr^{51} isotope of 30 days is then at variance with the accepted half life of approximately 60 days. Weinstein[14] addressed himself to this problem and observed that there is an in vitro "elution" from the red cell of approximately 1 per cent of the activity per day during the first 30-60 days. This constant elution has been observed in all survival studies done and by appropriate calculation can be shown to account for the "apparent" short red cell survival. The chromium attached to the red cells is still present in measured amounts of 1-2 per cent at 120 days. Thus the chromium tag persists for the life span of the erythrocyte.

The fate and excretion of the radioactive chromium has been studied by Ebaugh,[6] Finch[15] and the present authors. In experimental animals the urine at the end of 22 days accounts for 40 per cent of the chromium radioactivity administered. Using our method of incubating whole blood with the chromium, we have obtained similar rates and amounts of excretion in urine of the original radioactivity. The remainder resides in the reticuloendothelial system, i.e. liver and spleen. This residual activity in the spleen and liver has allowed for differential counting over both organs as compared to the sternal marrow. Jandl[5] has been able to utilize the differential rate of hemolysis to evaluate the site of red blood cell sequestration and anticipate therefrom prognosis following splenectomy.

The toxic effects of the metal chromium by itself are limited to the red cell. The chromium ion, if in excess of 30 gamma/cc of red blood cells, will cause a decrease in the normal red cell half life.[15] The changes produced by the chromium tag are revealed as abnormalities in the electrophoretic movement and glycolytic rate when the level of 10 gamma/cc of red blood cells is exceeded.[5] With the specific activity of 30-40 millicuries/mg. of chromium available today, this is not a problem since the amount used is 0.5 gamma or less/cc of red blood cells. This minute amount of chromium used in our red cell survival studies is far below that known to produce a significant biological alteration.

Radioactivity

Radioactive chromium[51] emits energy by virtue of its K capture roughly equivalent to beta rays (4.9 KV) and its gamma rays of 0.32 MeV in 8 per cent of disintegration. The latter activity of the chromium is counted as a gamma ray in the well scintillation chamber. The physical half life of the isotope is 28 days.

Finch[15] postulated, "Assuming the extreme situation in which all beta rays might be localized in a marrow 1500 ml. in volume, and an excretion of half of the initial dose, an injected quantity of as much as 6 microcuries per kilogram equivalent to about 0.3 roentgens/wk (r/wk.), should be permissible in the adult."

"Thus approximately 250 microcuries of chromium may be administered to reach an initial dosage equalent to 0.3 r/wk. and 390 microcuries if excretion is considered."

Ebaugh[6] has evaluated the same problem and is in general agreement with the above calculations. The possibility exists that in a hemolytic state excess radioactivity may remain in the spleen. In an analysis of this problem in dogs given aged red cells, Ebaugh has calculated that the spleen itself will receive 10 times the concentration occurring in liver and bone marrow so that the spleen will contain one-third of the original dose. The present authors have analyzed the radioactivity of two spleens in patients who had received chromium shortly before operation. The wet weight of the spleens contained 8.7 per cent and 25 per cent of the total original activity, respectively, with respective T½ values of 12 and 15 days.

"If one assumes a similar type of distribution in human subjects, an individual experiencing very rapid hemolysis of donor cells (i.e. 50 per cent or more in one day) who was given 320 microcuries, would be exposed to not more than 1.7 rep/week delivered to the spleen. The above calculations are conservative inasmuch as it is assumed that all the Cr^{51} going to the spleen remained there and was not cleared from this tissue and that no Cr^{51} was excreted."[15]

Our dosage of radioactivity used in these studies has been from 15 to 60 microcuries of chromium with an average of 30 microcuries. (The higher dosages were in the patients in whom splenectomy was contemplated).

Therefore, if it is agreed that 390 microcuries produces less than 0.3 roentgen equivalents physical (rep), then 30 microcuries will

deliver not more than 0.03 r/wk. A total dose delivered to the body during the entire activity period of the isotope (7 half-lives) would be 0.84 rep. Geometric calculations would then necessitate some alterations in both directions because of the smaller mass of the infant. Thus, using these figures as a basis for estimation, it seems fair to conclude that in none of the studies to be reported has the radiation delivered to the patient exceeded 1.0 roentgen. The total dose from such a diagnostic procedure then is considerably lower than that delivered by 1-2 minutes of cardiac and gastro-intestinal fluoroscopy.

Methods

The whole blood to be tagged with radioactive chromium is drawn into a heparinized siliconized syringe through a needle previously immersed in Arquad. The chromium is added and the contents gently rotated for 30 minutes. Ascorbic acid (50-250 mg.) is then added to convert the excess plasma chromium to the trivalent form. After 5 minutes, the whole blood is reinjected into the patient. A portion of the injected blood is removed and counted for use as a red cell mass measurement if needed.

A half hour is allowed for general equilibration. The first sample removed at that time is taken as 100 per cent. Subsequent samples are then removed as indicated. Activity is measured as counts/cc of whole blood due to the red cells in 1 cc of whole blood. This is obtained by subtracting the activity in the plasma from the activity in 1 cc of whole blood. With this technique we have not observed the 10-15 per cent fall in Cr^{51} activity observed by others during the first 24 hours after injection of the tagged red blood cells. We attribute this difference to the more gentle handling of the red cells in the procedure involved in their labeling.

Congenital Nonspherocytic Hemolytic Anemia

During the past several years "nonspherocytic hemolytic anemia" has been separated from the previously identified groups of congenital hematological disorders. This hemolytic anemia is characterized by macrocytosis, basophilic stippling, hepatosplenomegaly, and jaundice. Typically, the onset occurs in infancy and may simulate erythroblastosis fetalis. Using the available techniques of hematological analysis, this disorder can be differentiated from thalassemia, familial spherocytosis, the hemolytic diseases based on molecular abnormalities of hemoglobin, and acquired hemolytic disease. Evidence thus far presented suggests that it be considered as a clinical and pathogenic

entity. Dacie and associates,[16] Kaplan and Zeulzer, [17] and Crosby[18] have demonstrated by cross-transfusion studies that there exists an intrinsic defect of the red blood cells in this disease as in thalassemia, hemolytic anemia associated with abnormal hemoglobins, and spherocytic anemia. Thus far, however, the exact nature of this abnormality has not been elucidated. In most of the cases reported to date, evidence of a genetic basis has been discovered.

It is the purpose of this report to present two additional cases of congenital nonspherocytic hemolytic anemia. These patients have been shown to have a primary intracorpuscular defect as measured by red cell survival studies in the patients themselves and in normal persons.[36]

Case Reports

Case No. 1— (Hosp. No.) is a 6-year old female child. Moderate jaundice was present at 24 hours of age on March 14, 1949. The liver was palpable 4 cm. below the costal margin and the hemoglobin was 12.2 grams per 100 cc whole blood.

Increasing pallor became evident during the first four weeks of life. Iron therapy was begun after a hemoglobin of 6.6 grams per 100 cc was noted when the patient was 4 weeks old. Despite adequate medication, a reticulocytosis of 14 per cent and hemoglobin of 7.0 grams were still present at 3 months of age and she was readmitted for study at the University of Minnesota Hospitals.

Measurements of hemoglobin, reticulocytes, and study of peripheral smears of the parents and siblings were normal. Review of the family history did not reveal any previous significant difficulties except that the mother had a transient "anemia of pregnancy."

Laboratory examination demonstrated a hemoglobin of 7.2 grams per cent, a red blood cell count of 2.3 million per cubic millimeter, and a hematocrit of 21 per cent. The mean corpuscular diameter (MCD) was 8.0 mu and the mean corpuscular volume (MCV) was 91 cu. microns. Bone marrow and peripheral blood examination revealed a marked degree of basophilic stippling of the erythrocytes and normoblastic hyperplasia. The osmotic fragility was normal, beginning at 0.48 per cent and being complete at 0.32 per cent (the same as the control). Laboratory examination revealed a fecal urobilinogen level of 240 Ehrlich units (E.U.) per 100 Gm. The erythrocytic protoporphyrin was 105 gamma per 100 cc red blood cells (normal 27 to 38 gamma per cent). The urine coproporphyrin was 37.5 gamma per day (normal total for adults is 170 gamma per day). Test for porphobilinogen was negative. The serum iron was 92 gamma and the iron-binding capacity was 200 gamma/100 cc blood (normal 85 to 120 and 200 to 300, respectively). The direct and indirect Coombs tests were negative.

The patient continued to grow and develop normally despite a persistent anemia of 7 to 8 grams per cent Hb, and reticulocytosis of 10 to 20 per cent.

At 6 years of age she weighed 19 kilograms and was 114 centimeters tall (25th percentile according to the Iowa standards). The liver was palpable 3 cm. below the costal margin and the spleen was palpable at the left costal margin. There was a definite grade II systolic murmur in the pulmonic area which was considered to be "hemic" in origin by the pediatric cardiology staff. Her hemoglobin was 8.2 grams per cent, reticulocytes 16.3 per cent.

The hemoglobin electrophoretic pattern was normal. On a Price-Jones curve many macrocytes were observed. The Coombs test was negative after trypsinization of the red blood cells. No urinary hemoglobin was found. Serum iron was 55 gamma per cent. Plasma hemoglobin was less than 12 mg. per cent. Fecal urobilinogen was 1,000 E.U. per 100 Gm. of stool. Coproporphyrin was 95 gamma per day. A reversal of the urinary coproporphyrin isomers was present. Type III isomer comprised 90 per cent of the total urinary coproporphyrins, whereas in normal children and adults, type I is the predominant isomer. Other liver function tests, including cephalin cholesterol, thymol turbidity, and bromsulphalein excretion were normal. Toxicological examination of the urine was negative for lead and arensic. Bone marrow examination did not reveal any siderocytes or hemosiderin deposits.

A cross-transfusion study using radioactive Cr^{51} was done. The patient's blood cells, tagged with Cr^{51}, when transfused into a normal subject showed a marked reduction in red

cell survival time. Conversely, when normal blood cells tagged with Cr^{51} by the same technique were transfused into the patient they showed a survival time only slightly shorter than that characteristic of normal cells in normal persons.

Case No. 2— At 3 years of age this Chippewa Indian boy was referred to the University of Minnesota Hospitals for evaluation and therapy of hemolytic anemia.

Pallor, restlessness, and protuberant abdomen were first observed when he was 3 months old. His physician noted a severe anemia, with enlargement of both liver and spleen. The patient was treated with ferrous sulfate, vitamin B_{12}, liver extracts, and repeated blood transfusions without altering the course of the disease. Laboratory data revealed a persistent anemia of 6 to 8 grams hemoglobin per 100 cc, normal saline fragility studies, negative Coombs test, and a normoblastemia of 18 per 100 white blood cells. Bone marrow biopsy was reported as showing "erythroid hyperplasia." Clinical jaundice was not evident, but the persistence of the anemia suggested the possibility of hemolytic disease and a splenectomy was performed at Red Lake Indian Hospital, Minnesota, when the child was 9 months of age. The spleen was noted to be twice normal size and microscopic sections demonstrated "normal splenic architecture with red cell engorgement of the pulp."

Despite the splenectomy and transfusions at intervals of ten weeks, the hemoglobin level could not be stabilized. The patient was then transferred to the University of Minnesota Hospitals.

Physical examination revealed hepatomegaly, carious stunted teeth, scleral icterus, and minimal "bossing" of the frontal bone. The weight was 21 kilograms and the height 96 centimeters. The following laboratory data were obtained on admission: red blood cells 1.6 m/cu mm., hemoglobin 4.3 grams per cent, hematocrit 12 per cent, total white blood cell count 16,400 with 50 per cent neutrophils, 37 per cent lymphocytes, 6 per cent eosinophils, 6 per cent monocytes, and 1 per cent basophils. There were 25 normoblasts per 100 white blood cells. Reticulocytes were 2.5 per cent, platelets 200,000/cu mm. The sedimentation rate was 90 mm. per hour (Westergren). His red blood cell indices were: MCV 83 cu. microns; MCH 28 micromicrograms; MCHC 34 percent; and MCD 8.18 microns. The bilirubin was 1.3 mg. per cent total, of which 0.1 mg. was direct. The fecal urobilinogen was 233 mg. per 100 Gm. The erythrocytic protoporphyrin and coproporphyrin were, respectively, 71 and 3.8 gamma per 100 cc red blood cells (upper limits for normal children 40 and 2.0 gamma per cent, respectively). The serum iron was 308 gamma per cent (upper limit of normal 120-150). The following blood tests gave values within the normal range: hemoglobin electrophoretic pattern, alkali resistant hemoglobin content, osmotic fragility, cold agglutination, direct and indirect Coombs test, and sickle cell preparation. Additional studies that were negative included: serological tests for syphilis, thymol and cephalin flocculation, blood urea nitrogen (BUN), total and esterified cholesterol, serum chloride, sodium, potassium, carbon dioxide combining power, C-reactive protein, antistreptolysin titer, and Mantoux 1:1000 and 1:100 O.T. Similarly, no porphobilinogen, hemosiderin or hemoglobin was found in the urine which contained a normal concentration of coproporphyrin (102 gamma per twenty-four hours). Isomer studies were not done.

Hematological examinations of the parents and six siblings did not reveal any similar disorder. No pathological red cells or increased reticulocytes were noted on peripheral smears. One sibling had an iron deficiency anemia which responded promptly to simple ferrous sulfate therapy.

Thereafter, because he required 300 to 400 cc of whole blood every four weeks to maintain his hemoglobin and because we felt that acquired hemolytic anemia based on immunological mechanisms may rarely give rise to false negative results with the Coombs test, steroid therapy was tried. Cortisone initially in a dose of 150 mg. per day for four weeks, then 300 mg. per day for three weeks, and finally ACTH 50 mg. per day for six weeks were given. Despite the development of a marked "Cushing syndrome" and mild hypertension (140/90), the hemolytic process continued unabated.

Repeated red cell survival studies using radioactive Cr^{51} were undertaken and definitely demarcated an intracorpuscular defect. Finally, as in Case 1, the chromium survival studies of normal red blood cells in this patient gave half-life values slightly shorter than was the case in normal persons, indicated that an extracorpuscular mechcanism was contributing to the hemolysis. Consequently, an exploratory laparotomy was done in the hope of finding an accessory spleen, the removal of which we anticipated might ameliorate the hemolytic process. Indeed a large accessory spleen weighing 117 grams was found in the left upper quadrant in the bed of the spleen which had previously been removed. Microscopic study of the accessory spleen revealed only an increase in red pulp and large amounts of iron pigment in the perivascular areas. A liver biopsy done at the time revealed "marked hemosiderosis and minimal myeloid metaplasia."

Despite a temporary decrease in the requirement for transfusion following splenectomy, the hemolytic process quickly returned to its previous state. The child was finally discharged for care in his local community where he required transfusions of 200 cc of whole blood every four to six weeks to keep his hemoglobin above 6 grams.

Both patients had their red cells transfused into a normal recipient. The half-life of the radioactive Cr^{51} was 9 and 6 days, respectively. Thus this remarkable shortened life cycle definitely indicated the presence of an intracorpuscular defect.

Conversely, normal red cells when transfused into our patients exhibited a survival approaching the average normal value. The half-life values of the normal cells in the two patients were, however, shorter than the lowest normal values. Therefore, we were forced to conclude that both patients presented evidence of an extracorpuscular hemolytic factor as well as the intracorpuscular defect. That such was the case was indicated by the temporary abatement of the hemolysis in Case 2 following removal of his accessory spleen. These results are remindful of those of Lichtman[19] and associates and Smith[20] and coworkers who demonstrated that continued hemolysis in thalassemia major will produce a "hypersplenic" extracorpuscular abnormality contributing to the hemolytic process. In this light, the slight shortening of half-life of the normal cells transfused into our two patients is not surprising.

Discussion

The two case reports cited here must be classified with the group designated as nonspherocytic hemolytic anemia.[21] In both children the disease began in infancy and was due to moderate or severe hemolytic process. In both instances the laboratory features ruled out thalassemia, sickle cell disease, and acquired hemolytic anemia. The lack of a hereditary pattern, although unusual, has also been noted by Watson and Feinberg[22] and others.[16] Radioactive Cr^{51} red cell survival studies established the existence of an intracorpuscular defect as the basis for the hemolytic disorder. However, evidence was obtained that in these patients as in others whose hemolytic disease is due primarily to an abnormality of the red blood corpuscles, extracorpuscular factors may contribute to the total hemolytic process. Perhaps the macrocytosis noted in our study requires comment. Certainly it is not unique to our cases. Haden[23] and Holliday [24] have made pointed notation of this feature in other cases. Macrocytosis and increased mean corpuscular volume greater than 100 cu microns have been noted in each of the clinically affected cases of nonspherocytic hemolytic anemia. Occasionally reports of extremely large cell volumes ranging up to 120 cu microns have been noted. Lipton and associates did have two cases with normal MCV. However, neither was established as an intracorpuscular defect by survival studies. Certainly because of the relatively large size of immature red cells and the presence of reticulocytosis in our cases we cannot be certain that the macrocytosis was not a function of the immaturity of some of the cells in the peripheral blood. Regardless of its basis, macrocytosis is a clinical feature characteristic of nonspherocytic hemolytic anemia, and may in some way be associated with the intracorpuscular defect demonstrated to exist in these cases.

The presence of increased fecal urobilinogen, reticulocytosis, and abnormal red cell survival studies were ample evidence for the presence of a continued hemolysis in these patients. In our Case 1, however, low serum iron and increased erythrocytic protoporphyrin were noted. Kaplan and Zeulzer[17] similarly noted serum irons in the 30 to 50 gamma per cent range in his original three cases. Crosby[18] has also commented upon the paradoxical lack of siderocytes and normal serum iron in his patients. The punctate basophilic stippling in the erythrocytes has been shown not to be iron in Case 1 and in others. These observations are characteristic of a "chemical iron deficiency" despite the apparent and documented excessive hemolysis. In these cases the reticuloendothelial system must retain iron deposits in a particularly insoluble form. Such a "hemosiderin complex" conceivably could completely remove from the "metabolic pool" a disproportionate share of iron and thus render the total system "iron deficient." Such an hypothesis deserves further investigation.

In Case 1 a study of the capacity of the body to clear iron tagged with radioactive iron was done. Complete disappearance from the plasma of the radioactivity as early as two hours after injection was noted. Crosby and others likewise have noted such rapid clearance values to be characteristic of their patients. The accelerated rate of removal of this tagged iron-globulin complex reflects increased utilization by the hyperplastic erythroid system.

Acquired Hemolytic Anemia

The clinical descriptions and experiments of this entity by Chauffard and Widal and later by Dameshek and Schwartz[18] have stood as classics in our understanding of this disorder. By producing a hemolysin to the red cells in rabbits by heterologous transfusion, Dameshek[25] was able to reproduce experimentally the characteristic findings of acquired hemolytic anemia. He graphically demonstrated in this manner that the hemolytic anemia so produced was of a spheroidocytic nature and had an increased osmotic fragility. With the introduction of the Coombs test by Coombs, Mourant and Race[27] sensitized red blood cells were easily distinguished.

Despite the clarity commonly found in the separation of acquired hemolytic anemia and familial spherocytic hemolytic anemia, overlapping and confusion still exist. The spheroidiocytes are quite typically present in the acquired hemolytic anemia and occasionally the difficulty is considerable in differentiating idiopathic acquired hemolytic anemia

from familial hemolytic anemia in childhood. As a result of the marked spheroidocytosis, the saline fragility test often demonstrates an enchanced susceptibility to osmotic hemolysis. The Coombs test, when positive, is of fundamental significance. A positive Coombs test done even with special techniques cannot always be demonstrated in these patients. A family history and/or documentation of spheroidocytes in the family is helpful; but not all children with congenital microspherocytic hemolytic anemia will demonstrate evidence of genetic transmission. The comparison between the two entities is outlined in Table I.

TABLE I

COMPARATIVE CHARACTERISTSCS OF ACQUIRED HEMOLYTIC ANEMIA AND SPHEROCYTIC FAMILIAL HEMOLYTIC ANEMIA

	Familial Hemolytic Anemia	*Acquired Hemolytic Anemia*
Spherocytes	Always present	Commonly present
Splenomegaly	Always present	Usually present
Osmotic Fragility	Increased	Commonly increased
Coombs Test	Rarely positive	Rarely negative
Family History	Regularly	Rarely present
Crises		
Fever	Present	Present
Infection	Present	Present
"Aplastic"	Frequently	Frequently
CROSS-TRANFUSION STUDIES		
Normal Cells into Patient	Normal survival	Decreased survival
Patient into Normal	Decreased survival	Normal survival
Splenectomy	100% cure of clinical disease	50% improvement
Cortisone	No effect	50% effective

During the past three years, two children with hemolytic anemia have been diagnostic problems because of the absence of a positive Coombs test. In both patients the indirect Coombs test was done using trypsinized normal cells and using acid pH with both warm and cold temperature environments. In both children all these were negative. The diagnosis was, established however, by the use of the chromium cell survival method. The patients were transfused with normal whole blood which was tagged with Cr^{51}. In both the red cell survival was markedly decreased. The first patient had an apparent red cell chromium half-life of only 10 hours and the second had a cell survival of 6 days. Treatment with cortisone in each instance was rewarded with a diminution of the hemolytic rate and return to a normal hemoglobin.

Case No. 3.

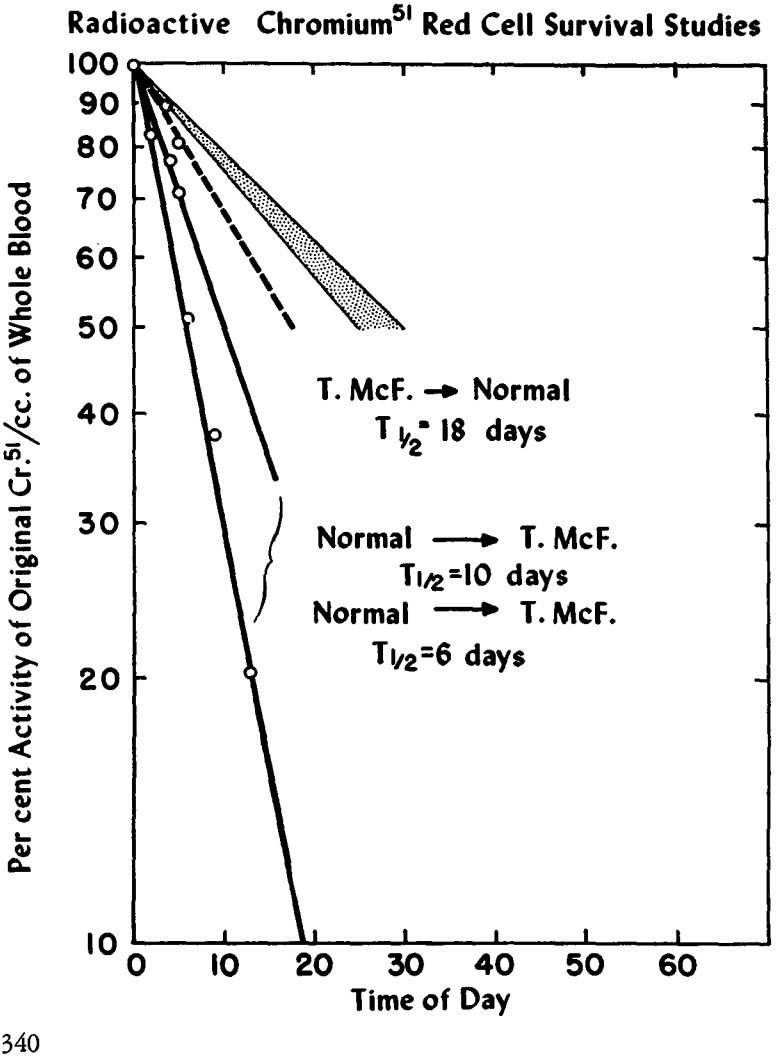
. was apparently well until 20 months of age when he displayed lethargy, pallor and anorexia. At Fort Devans Army Hospital, Massachusetts, his condition was diagnosed as iron deficiency anemia for which he received iron therapy. A large spleen and heart murmur were said to be noted at that time also. At about two-to-three month

intervals episodes of pallor, restlessness, dark urine, and light stools occurred. These lasted for about two to three weeks.

The last episode began four to five days prior to admission. Because of his low hemoglobin and splenomegaly, he was referred to the University of Minnesota Hospital for diagnosis on July 21, 1955.

The pertinent points of physical examination included pallor of the conjunctiva and retina, a systolic murmur heard over the entire precordium. Liver was palpable 4.5 cm. below the right costal margin, the spleen was palpable 10.5 cm. below the left costal margin. Lymph nodes were within physiological limits. (Fig. 1.)

FIGURE ONE



Laboratory results: Hemoglobin was 5.5 grams per cent and the reticulocytes were 10.4 per cent on admission. The bilirubin was 1 mg. per cent and the reticulocytes rose to 18.5 per cent. The fecal urobilinogen determination revealed that there were 450 EU/100 Gm. Serum iron was 160 gamma per cent. Peripheral blood examination demonstrated an increased polychromasia. The bone marrow examination revealed that there were 62 per cent normoblasts with many mitotic figures. The mean corpuscular diameter was 7.4 micra. A normal saline osmotic fragility test was obtained.

The hemoglobin electrophoretic pattern was normal and the alkaline denaturation test was negative. Similarly, test for sickle cell by incubation was negative. Direct and indirect Coombs tests were negative on repeated occasions. Special attempts using trypsinized red cells were done to sensitize or develop a positive Coombs test in the patient's serum. These were all negative. The possibility of porphyria was considered, but the urinary coproporphyrins and porphobilinogen were normal and there was no light sensitivity. The urine was negative for hemoglobin, and no abnormal plasma hemoglobin was found. Heterophile agglutinations and cold agglutinins were both negative. Urinalysis was negative as were the Mantoux and histoplasma skin tests. Total and fractional proteins were normal.

A circulating agglutinin was noted in the patient's blood. This was demonstrated by using his acidified serum to agglutinate 8 of 10 normal O Rh positive blood cells tested.

A red cell chromium life span study was then done. We injected normal red cells tagged with Cr^{51} into this patient when his hemoglobin had fallen and followed the survival of these tagged red cells by measuring the radioactivity of Cr^{51}. A half life was obtained of 7 days, normal being approximately 26 to 30 days. (Fig. 1.)

Steroid therapy was begun on September 7, 1955. His hemoglobin after he was placed on therapy of this nature rose from 9.8 to 12.4 two weeks later. The reticulocytes which measured between 8 and 15 per cent prior to therapy numbered 3 to 7 per cent before discharge. On the 6th of October his hemoglobin was 12 grams per cent and reticulocytes were only 2 per cent. Further confirmatory evidence of a reduction in amount of hemolysis was obtained by the fecal urobilinogen studies on September 13-17 at which time there were only 102 Ehrlich units per 100 grams and on September 24 when 104 Ehrlich units per 100 grams were also noted.

During the next seven months, the cortisone was gradually reduced. The spleen was not palpable during this time and the hemoglobin remained at 12 Gm. per cent. However, 5 weeks after cortisone was discontinued, splenomegaly, reduction of hemoglobin and increased reticulocytes were noted.

During his second hospital admission, repeat radioactive chromium analysis was done. Normal cells, when transfused into the patient, demonstrated an apparent chromium red cell half life of 10 days. When the patient's cells were transfused into a normal, a half life of approximately 20 days was obtained. This definitive study demarcated the hemolytic anemia as an acquired extracorpuscular defect.

Splenectomy was accomplished without difficulty and the subsequent course has been extremely benign. Hemoglobin remains normal and the reticulocytes and fecal urobilinogen are within normal limits.

Case No. 4. (Hosp. No. This 2½-year old infant had been well until the present illness. The child had a mild cough and cold with no fever 5 days before admission to the University of Minnesota Hospitals. She was treated for this by her private physician with "Robitussin" and hydriodic acid. Mild hive-like reaction was noted on the third day before admission. Two days before admission the child suddenly developed a fever of 103 and the mother noted a pink stain on the diaper. This patient was then seen by her physician who was not able to note any cause for the fever and gave the child achromycin. By the following day the child was slightly pale and dark urine was noted. On the day of admission the physician noted marked pallor and moderate jaundice. Because of this the child was transferred to the University of Minnesota Hospitals.

The past history in the family is interesting in that the mother 3 years ago had splenomegaly, an anemia of 10 grams per cent, a thrombocytopenia and a leukopenia. This was diagnosed as a "hypersplenism" and she was seen at the Mayo Clinic and at the University of Minnesota. In all her examinations there was no evidence of spheroidocytosis. However, a cell fragility recently demonstrated increased osmotic fragility (beginning at 0.58 per cent). Splenectomy was performed 2 years ago and resulted in a prompt rise of the platelets and the white cells. However, she has continued to have an elevated reticulocytosis although her hemoglobin remains stationary between 10 and 12 grams.

Physical examination of the infant revealed a well-developed 2½-year old who was in no apparent distress but who demonstrated marked pallor and definite jaundice of the skin and of the sclera. The spleen was not palpable and the liver was palpable at the costal margin. Otherwise, the physical examination was entirely normal.

Hemoglobin concentration upon admission to the private hospital was 8 grams per cent. On arrival at the University of Minnesota Hospitals 3 hours later, the hemoglobin

was 6 grams per cent. Further laboratory work on admission revealed a Coombs test that was negative by direct and indirect methods. A trypsinized Coombs indirect test was negative. Additionally, cold and warm hemolysins and acid hemagglutination using trypsinized and normal cells were negative. The patient had a plasma hemoglobin of 370 mg. per cent. The urine hemoglobin measured 220 mg. per cent. Despite this evidence of hemolysis, the reticulocytes measured only 3 per cent. Bone marrow did not demonstrate a normoblastic hyperplasia. The normoblasts numbered only 10 per cent of the total cells in the bone marrow. Shortly after admission the child received 100 cc of packed cells of recently drawn blood. These red cells were tagged with radioactive chromium.

Results of the radioactive chromium survival revealed that within 10 hours 50 per cent of the transfused normal cells had been destroyed. This marked reduction in the survival of the normal cells transfused into the patient enabled us to document and identify this hemolytic process as one of an acquired hemolytic nature. Further confirmation of this impression was obtained when, after cortisone of 35 mg. every 6 hours was instituted, there was a marked and rapid change in the rate of hemolysis. The rate of the previous sharp decline changed to a more gradual, although still increased above normal, rate of hemolysis. Continued survival studies were done during the next several days and demonstrated gradually lessening rate of hemolysis.

However, the child did require another transfusion of whole cells 24 hours after institution of cortisone because of the low hemoglobin concentration. Subsequently the child has had a return to normal of the hemoglobin with normoblastic hyperplasia of the bone marrow above 60 per cent and a reticulocytosis of 20 per cent. At the present time she is being followed to see whether or not this hemolytic anemia will be that of an acute nature or will progress to a chronic form.

Emphasis must be made here that the diagnosis of acquired hemolytic anemia was made with some assurance and rapidity in a clinically confused state. First, this child could have been suffering from familial spherocytic hemolytic anemia in view of the mother's history even though the mother continued to have evidence of hemolysis despite splenectomy. Accessory spleens must still be considered a basis for continued hemolysis in familial hemolytic anemia. Second, several specialized Coombs tests were done which were negative. The chromium study, therefore, provided essential clues since the diagnosis might have been considered to be familial hemolytic anemia.

This problem in converse manner has also been observed on our wards. The case of J. S., No. 5, conceivably could have been considered to be acquired hemolytic anemia without positive Coombs test since his family study was entirely negative for familial hemolytic anemia. Chromium study established the diagnosis of congenital intracorpuscular defect (i. e. s-heroidocytosis).

Case No. 5, . (Hosp. No. . This 2-year old male child was admitted to the University Hospital on July 9, 1955 because of pallor. John had had measles 1 month prior to admission and since then had penicillin injections for "sore throat". For the two weeks prior to admission he was febrile, lethargic and anorexic.

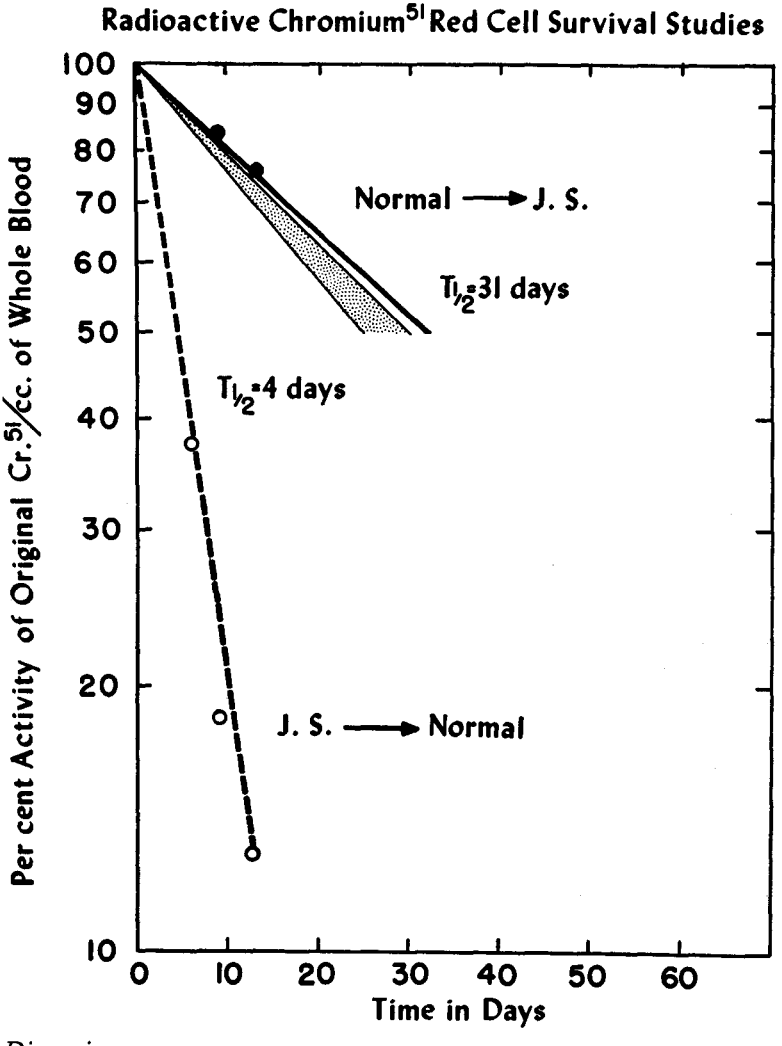
On admission, pallor, lethargy and irritability were noted. The liver was palpable at the right costal margin and the spleen was very firm extending 3 cm. below the left costal margin. Temperature was 104 on admission. Blood culture at that time revealed a Type VI pneumococcus and nose culture contained pneumococci. X-ray of the chest demonstrated right upper lobe and lower lobe pneumonitis. Therefore, a diagnosis of sepsis and pneumonia were documented.

Hematological studies included: hemoglobin 6.4 grams per cent, reticulocytes 18.3 per cent, bilirubin 0.6 mg. per cent, negative heterophile test and Coombs test, increased cell fragility (beginning at .60), and MCD of 6.4 microns and normoblastic hyperplasia in the bone marrow. Peripheral blood smears, studied by Dr. R. D. Sundberg, from both parents, both maternal grandparents, 3 brothers and 1 sister, 2 aunts and 3 uncles, were all negative for evidence of familial hemolytic anemia. Historical review and examination of the parents and siblings for splenomegaly were entirely negative.

Therefore, the critical familial elements necessary for substantiating a diagnosis of familial hemolytic anemia were absent. Consideration was given to the fact that the acute septic process and the preceeding measles episode might have produced an acquired hemolytic anemia.

The problem was clearly settled by the use of the tagged chromium cross transfusion study. When the patient's cells were transfused into a normal, the $T\frac{1}{2}$ Cr^{51} was 4.5 days; conversely when normal cells were transfused into him, the patient's $T\frac{1}{2}$ Cr^{51} was 31 days. That this was not acquired hemolytic anemia and that it was a type of congenital spherocytic hemolytic anemia is brought sharply into focus by the data obtained. (Fig. 2).

FIGURE TWO



Discussion

Mollisson[28] and Read[3] have demonstrated the dynamics of normal cells transfused into a patient with acquired hemolytic anemia. Similarly, in the two patients outlined here the diagnoses were confirmed by radioactive chromium red cell survival.

Conversely, the diagnosis of acquired hemolytic anemia was strongly suggested by Case No. 5 because of the complete absence of signs and/or symptoms in the family. The definition of an intracorpuscular defect was supplied by the radioactive chromium red cell transfusion study.

Therapy of Acquired Hemolytic Anemia with Nitrogen Mustard

Although two of the children with acquired hemolytic anemia recorded above have responded in excellent manner to the regimes of cortisone and/or splenectomy, we have two additional children in whom these therapies, although influencing the disease, have not resulted in persistant relief. Both of the patients had developed signs and symptoms of severe hypercotisonism during the period of prolonged treatment. C. A. had been on steroid medication for 3½ years and the slightest reduction of her dosage resulted in reappearance of frank hemolysis and anemia. D. B. had a convulsion probably attributable to the steroid treatment.

In an attempt to control these desperate situations, both chidren were given nitrogen mustard. Nitrogen mustard (HN_2) has been used by Dameshek,[29] Myer,[30] and Sievers [31]. Only in Dameshek's case was limited success achieved in alleviation of the idiopathic acquired hemolytic anemia.

The successful use of nitrogen mustard in nephrosis clinically and experimentally has been theoretically considered as being due to interference with the immune response. Therefore, because of the gravity of the clinical conditions and the inadequacy of hormone therapy together with the occasional remissions produced by HN_2 treatment in nephrosis, intravenous nitrogen mustard therapy was tried.

Case No. 6.

(Hosp. No. . This 2-year old girl was first noted to have pallor, slight jaundice, orange colored urine and a hemoglobin of 7.0 gm. per cent in July, 1952. Moderate reticulocytosis and elevated total bilirubin were noted. Because of persistent falling hemoglobin, she had a splenectomy in October, 1952. This did not prevent further hemolysis. Frequent and heroic transfusions were required to maintain hemoglobin. In December, 1952 she was given a trial of ACTH and cortisone without success. An exploration for accessory spleens was also unproductive.

She was first seen at the University of Minnesota Hospitals on February 18, 1953 at which time because of a positive Coombs test, reticulocytes of 10 per cent, and an increased fecal urobilinogen, a diagnosis of acquired hemolytic anemia was made. Despite this her MCD was 5.6 microns, considered to be diagnostic of familial hemolytic anemia. She was placed on therapy of 200 mg. of cortisone per day which temporarily produced a remission. The cortisone could not be discontinued, however, because of a gradual fall in hemoglobin with reduction in dosage.

She was maintained on cortisone, (50 mg./day) from April until June of 1953. Then because of a further gradual fall in hemoglobin, despite continued cortisone therapy, ACTH was given intramuscularly 20 mg./day.

The therapy of ACTH was continued for 1 year. During this time any gradual re-

duction by as little as 2 to 5 units would precipitate jaundice, dark urine and falling hemoglobin. Because the excessive hemolysis necessitated continuing therapy despite the fact that the child had a sevre cushingoid appearance, further methods of management were considered. Nitrogen mustard was used then in the hope of ameliorating the need for steroids which had been given for 3 years.

The first course of nitrogen mustard, 0.4 mg./kg., was given intravenously on December 17, 1954. Following this, there was a marked reduction in the fecal urobilinogen from over 300 mg./day to approximately 75 mg./day. All during this time the ACTH was continued as before. However, after 4 months had passed, the hemoglobin began to gradually decrease to 10 gms. per cent, and the reticulocytes had become elevated from 2 per cent to 4 per cent. Therfore, nitrogen mustard was given and a reduction in the fecal urobilinogen and a rise in the hemoglobin was again noted.

In June, 1955 because of an allergic reaction to ACTH, she had to be placed on cortisone therapy. She continued in this manner for the rest of 1955 and in January of 1956 she was admitted and given a third course of nitrogen mustard therapy, 0.4 mg./kg. intravenously, divided over the period of 2 days. At this time her fecal urobilinogen was markedly elevated. The reticulocytes were elevated. Following the use of the nitrogen mustard, the fecal urobilinogen became normal and reticulocytes were reduced to below 1 per cent. This was the first time in 3½ years that the child's reticulocytes had been within the normal range as well as the first time the fecal urobilinogen was measured within the normal range.

During the next several weeks the cortisone was gradually discontinued so that in May of 1956 she received her last dosage of cortisone. Since then she has not required any further cortisone or ACTH. Her hemoglobin has remained stationary, about 12 to 13 gms., and her reticulocytes have never risen above 1 per cent.

Of great interest also is the fact that her Coombs test which was positive every time in which it was tested, finally became negative six months after cortisone was discontinued. At the present time the child has a negative direct and indirect Coombs and has a normal fecal urobilinogen, hemoglobin and reticulocyte count.

The Cr^{51} auto-transfusion studies in this patient demonstrated an exceedingly rapid rate of hemolysis ($T½$ of 2 days) in October, 1954 prior to the first HN_2 therapy. Before the third course of nitrogen mustard was given, the Cr^{51} $T½$ was 15 days. Several months after the latter course of nitrogen mustard the Cr^{51} $T½$ was within normal limits ($T½ = 30$ days).

Case No. 7.

(Hosp. No . was admitted to the University Hospitals June, 1954 because of an acquired hemolytic anemia. He was treated at the Duluth Hospital with 1500 cc of whole blood and because the hemoglobin decreased preceptiously, a splenectomy was done then. Microscopic examination of the spleen which weighed 210 gms. revealed that there was interstitial hemorrhage of a uniform type within the splenic tissue. The malpighian bodies were not abnormal and there were two small accessory spleens. Shortly after the splenectomy the hemoglobin decreased to 6.0 gms. Therefore he received another 500 cc of blood on June 4 and was referred to the University Hospital on June 7. Upon physical examination the liver was not palpable and cervical lymphadenopathy was not remarkable.

Laboratory examination revealed a hemoglobin of 10.2 gm. per cent, red cells 3.2 million per cu mm. Hematocrit was 28 per cent. Indices were as follows: MCV 87 cubic microns, MCH 32 micromicrograms, and MCHC 26 per cent. The Coombs test was positive by both direct and indirect methods. Reticulocytes were 2.0 per cent. He received a transfusion on June 15, 1954 and cortisone therapy was instituted. An excellent response was maintained until August when the hemoglobin began to decrease as the cortisone was reduced to 10 mg. a day.

He was re-admitted for the second time on Sept. 24, 1954, because of the recurrence of the anemia. At this time the hemoglobin was 3.0 gm. per cent. Further laboratory examination revealed the following: bilirubin was 1.3 mg. per cent total with a one minute reaction of 0.2 mg. per cent. Total serum protein, Na, and Cl were normal. Mantoux, histoplasmin, heterophile, and cold agglutinations were all negative. The Coombs test has remained significantly positive throughout the entire course of his illness. The first serum iron obtained was 271 gamma per cent on Sept. 29. Plasma hemoglobin was 48 mg. per cent on admission and he was excreting 870 mg. of fecal urobilinogen per 100 gms. of stool. Following transfusion and reinstitution of large doses of cortisone, the hemoglobin could be maintained at levels between 12 and 16 gm. per cent.

He was readmitted to the hospital for the third time on March 2, 1955 after being maintained on cortisone therapy of gradually reducing doses of 100 to 75 mg. per day. This readmission was necessitated by a generalized seizure. The pneumoencephalogram was normal and no specific etiology was found for the seizure. There has been no further

recurrence of this difficulty and we have attributed this seizure to the high doses of cortisone that were required.

Following the convulsion which occurred in March, 1955 two courses of nitrogen mustard were given in an attempt to alleviate the hemolytic process. The first nitrogen mustard was given on March 23 and the second on April 20. Following both of these courses, definite clinical and hematological evidence of remission was observed. The first nitrogen mustard was followed by a reduction of the fecal urobilinogen from 600 mg. per day to less than 100. This decrease in fecal urobilinogen persisted for one month. The hemoglobin during this time rose to 12.0 gms. per cent. The reticulocytes which were 4 to 6 per cent previously were reduced to approximately 1 per cent. However, one month after the nitrogen mustard course was given his hemoglobin began to fall and the reticulocyte count became elevated. He was given 500 cc of blood and a second course of nitrogen mustard. At this time his reticulocytes fell slightly and the hemoglobin rose again. However, because of the recurrence of hemolysis, several weeks after the second course of nitrogen mustard, Meticorten® (20 mg. a day) was reinstated. Following this his hemoglobin remained stationary.

In the summer of 1956 the Meticorten® was gradually reduced. He developed what was considered a post-cortisone pseudorheumatism syndrome consisting of pain in his arms and legs and irritability for several days.

During this fifth hospitalization from August 30, 1956 to Sept. 9, 1956 he had a fairly stable hemoglobin of approximately 12.0 gms. per cent and reticulocytes of 2 to 5 per cent. During this stay his chromium red cell survival study was done for the first time and demonstrated a reduction in the red cell T½ survival to 13 days.

He was discharged and returned one month later for the last hospitalization at which time he was noted to have a severe anemia of 6.5 gms. per cent Hb. Shortly after admission a chromium red cell survival study was done in which the patient's own cells were tagged with radioactive chromium. Three days after the start of this red cell survival, the activity of chromium had fallen to 500 and two injections of nitrogen mustard were given. The red cell chromium survival was started in Oct. 27 and the nitrogen mustard was given on Oct. 29 and 30. It was apparent from the red cell survival study that there was a definite decrease in the rate of hemolysis. For a few days it appeared that the recticulocytes were going to correlate with this reduction in the hemolytic rate. On admission his reticulocytes numbered 58.6 per cent which on subsequent dates were as follows: on Oct. 29, 31 per cent; on Nov. 1, 20 per cent, and on Nov. 2 were 5.8 per cent. This last reticulocyte count was noted three days following the nitrogen mustard therapy. A return of the reticulocytes to 13 per cent and then to 33 per cent and 45 per cent on Nov. 9, 1956 was noted. During this period his hemoglobin did rise but never above 8.2 gms. per cent. In common with the reduction in reticulocytes and improvement in hemoglobin concentration was a fall in the fecal urobilinogen from 116 mg. per day before the nitrogen mustard, to 43 mg. per day four days following and thereafter to 62 mg. per day in early November. However, because no marked persistent improvement had been obtained, we decided to discharge him to his home. Meticorten® 15 mg./day was reinstituted.

Because of the "cure" produced by nitrogen mustard in the first patient and the reduction in the hemolytic rate as measured by the fecal urobilinogen in the second patient, an attempt was made to elucidate the mechanisms responsible.

The theoretical modes of action considered were two-fold. First, a decreased production of the red cells capable of being sensitized and a resynthesis of "different" red cells antigenically was considered. Second, a decrease in the "sensitizing" and erythrophagocytic activity of the reticuloendothelial system was postulated.

Therefore, during an episode of increasing hemolysis, a chromium red cell survival study was done using patient's cells in himself. By the fourth day of the chromium study the patient's apparent red cell chromium survival had been reduced to 50 per cent. On that day and on the fifth day he received 0.2 mg/kg HN_2 intravenously. Concomitant with this therapy and for the next several days his hemolysis, as measured by the chromium survival, returned to a normal rate. It would thus appear that of the two hypotheses outlined above, the latter appears more likely.

Discussion

During the past decade the advances in diagnosis and treatment of hemolytic anemia have been profound. Pauling's[32] brilliant demonstration of the molecular abnormality of the sickle cell hemoglobin has evoked ever-increasing interest in electrophoretic analysis in all hemoly-

tic anemias. Coombs, Mourant and Race[27] have perfected an extremely sensitive anti-sera capable of identifying red cells in acquired hemolytic anemia. The remissions produced by steroid therapy have been well documented by Dameshek[33] and others.

Despite the significant insight into hemolytic anemias revealed by these methods, clinical practice continues to provide cases of hemolytic anemia in which diagnosis is difficult and treatment inadequate. The universality and adaptability of the chromium method for analysis of red cell life span have provided an excellent adjunct to our diagnostic armamentarium. With the radioactive chromium method the dynamics of the life span of the erythrocytes can be readily delineated.

The syndrome of "non-spherocytic hemolytic anemia" as was demonstrated here represents an ideal situation in which the intracorpuscular defect can be established by the use of chromium red cell cross transfusion survival studies. The diagnostic difficulties encountered in our two patients could not have been resolved without great difficulty had not recourse been made to cross transfusions with Cr^{51} tagged red blood cells. Except for evidence of increased hemolysis no significant intracorpuscular defects were observed. The first patient was originally thought to have a peculiar form of iron deficiency anemia. The second patient was considered to represent a toxicological problem such as lead poisoning because of the basophilic stippling or alternatively an immunological acquired hemloytic anemia. Indeed, he received several months of ineffective steroid therapy because of the latter possibility.

The diagnosis of acquired hemolytic anemia was easily established in (Case No. 3) and (Case No. 4). The rapid disappearance of the normal cells transfused into these patients effectively delineated the pathogenesis of the hemolytic anemia. Therapy was instituted on the basis of this characteristic pattern and the anticipated remissions were obtained. This was accomplished despite the absence of a positive Coombs test and despite the presence of a hemolytic anemia occurring early in infancy which was suggestive of a congenital defect.

The successful use of HN_2 in therapy of acquired hemolytic anemia might be considered fortuitous. The documented improvement in the patient's own erythrocytic life span following and even during nitrogen mustard therapy provides an essential link in establishing the causal relationship. Such examples provide evidences for the continued need for a simple effective means of estimating red cell survival.

The choice of a method resolves around several considerations. Foremost, there must be a freedom of use that allows universal study of red cell life span in necessary situations. The limitations necessarily imposed by the Ashby method of differential agglutination would have made several survival studies herein outlined impossible. The ability to study red cell survival in all clinical situations is a most distinct advantage of the chromium methods. In every situation the Ashby method is more limited in applicability than is the chromium technique.

Second, the reduction of the life span of the patient's erythrocytes must on many occasions be studied in the cells' own environment. The ability to analyze the effects of therapy (nitrogen mustard and splenectomy) of the patient's red cells in his own circulation can be done only with radioactive Cr^{51}. This adaptability to diverse situations represents a unique attribute of this method.

A third consideration is that the phenomenon associated with the intrinsic disease process should not have any effect on the technique of measuring cell survival. The Ashby method is that of counting the remaining cells after specific agglutinins are added. The panagglutinin spontaneously present in acquired hemolytic anemia can produce false agglutination of the cells that should be unagglutinated. The chromium life span studies do not have this cause for error.

Fourth, chromium red cell survival may be done with a minute amount of injected blood (i.e. 1-2 cc) whereas the Ashby technique requires a large transfusion of a specific type cell. Furthermore, in measuring survival in normals with the Ashby technique, pretransfusion phlebotomy is required to maintain normal red cell equilibrium.

A criticism of the chromium red cell survival method is the elution of the chromium from the cell. This has been demonstrated repeatedly to be constant and represents during the first 60 days about 1 per cent of the chromium daily. Several authors [3, 4, 6] have examined this problem and have arrived at the same rate of elution. In computation of the actual average red cell survival from the chromium "apparent half life," a variation in the half life elution rate of from 40 to 70 days will produce essentially little change. Thus, if reference to average life survival is made with a T½ of chromium of 10 days, the extremes of the rate of elution will produce a calculated "true" survival of 30-45 days only.

However, in all of the examples given in the above, the average

"true" life survival was not used. Instead, attention was paid only to the relative *alterations* of the Cr^{51} T½ time. Thus the distinct disadvantage of the variable rate of elution from one cell population to another and from one individual to the next, does not disturb the evaluation of the dynamics of the red cell destruction.

During the past few years all use of radioactivity has become suspect. The amount of radiation given in these studies are well within limits prescribed by the National Research Council. In consideration of the small amounts of radiation it must be remembered that all of the individuals studied were affected with a serious disease process. These procedures may be favorably compared with diagnostic fluoroscopy. The diagnosis to be obtained and the possible therapeutic implications thereby gained significantly outweight the somatic risks.

Recently, on the basis of certain theoretical calculations[35] a panel of five geneticists has suggested that between 5-50 r delivered to the *general* population throughout the first 30 years of life will produce a doubling of the mutation rate. All of these studies, as does every single chest film, dental film and change to higher altitude, utilize a portion of the "genetic reserve." We are not conducting studies on the general population, however; and, the utilization of some of the "genetic reserve" must also be evaluated in the light of the benefits to be observed from this study.

Summary

1. A method of analyzing red cell survival by utilizing radioactive Cr^{51} has been presented. The advantages included in this system are, (a.) that an accurate estimate of red cell survival may be obtained in a comparatively short period of time, (b.) that the destruction rate of the patient's own red cells in their own natural "milieu" can be determined, (c.) that the analysis may be made even in the presence of known agglutinating activity of the patient's serum, and (d.) that there is no antigenic limitation to the use of cell survival studies.

2. "Non-spherocytic hemolytic anemia" has been described in two families by this method. The essential nature of this defect as an intracorpuscular defect has been elucidated by this method as described. An extracorpuscular defect contributes to the hemolysis in patients with non-spherocytic hemolytic anemia.

3. The diagnostic usefulness of the Cr^{51} has been defined in idiopathic acquired hemolytic anemia.

4. The use of nitrogen mustard in the treatment of idiopathic acquired hemolytic anemia has been described. A possible mode of action of HN_2 in ameliorating the destruction of the red blood cells has been suggested.

The authors wish to acknowledge the aid and stimulation provided by Dr. James Marvin under whose A.E.C. authorization the chromium was obtained, and by Dr. Raymond Read who originally introduced us to this method. To Dr. R. D. Sundberg whose many interpretations of peripheral smears and bone marrows are included here, and to Professor John Anderson for his discussions, many thanks are due.

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Staff Meeting Report

Injuries to the Facial Skeleton*

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In our traumatic era the facial skeleton is disorganized more frequently than most segments of the body framework. It is probably true that nasal fracture leads the entire list. Most nasal fractures are realigned and supervised as an out-patient activity. Only those that are more severe and those requiring general anesthesia for reduction are admitted to the hospital and included in the usual operative statistics. With this modifying fact in mind the following figures are indicative of the five year occurrence of facial skeletal injury on four services of the Department of Otolaryngology. They are divided anatomically into nasal, mandibular, maxillary, malar, and combined complex fractures.

Facial Skeletal Fractures
1952-1956 Inclusive

	Nasal	*Mandibular*	*Maxillary*	*Malar*	*Combined-Complex*
Service I	13	53	6	13	26
Service II	72	111	24	45	--
Service III	104	98	11	49	28
Service IV	93	27	3	29	26
Total	282	289	44	136	80

The skeletal complex of the face is formed by the union of three unpaired bones with seven paired bones.

The largest of the unpaired bones is the mandible. It supports the lower facial third and articulates with the skull base in the glenoid fossae of the temporal bones. The vomer bone and the ethmoid bone

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form the bony nasal septum and enclose the nasal vault at the cribriform plate. The lateral aspects of the ethmoid bone are honeycombed pneumatic labyrinths that support the medial aspects of the orbital content bilaterally against their paper-thin bony lamina. Nestled forward between the anterior edge of the ethmoidal labyrinths and the frontal processes of the maxillae are the lacrimal bones. Atop the frontal process the pyramid of the central third of the face is closed by the nasal bones as they join on the supportive ridge of the middle or septal plate of the ethmoid. The frontal processes of the maxillae are strong in this support but weaken laterally on the infraorbital margin where they abut the long, slender, overlapping medial processes of the malar bones. These latter bones, often termed zygomae, are sturdy blocks lying against the lateral-superior surface of the maxillae and being as one with them in enclosing that aspect of the maxillary sinuses. The malar bones unite at the upper lateral orbital boundaries with the frontal bones. Strong, archlike processes extend posteriorly to join with others from the temporal bones to form the malar arches. These arches give firm attachment to the masseter muscles while beneath them sleeve the bellies of the temporal muscles to attach to the coronoid processes of the mandible. Inferiorly the strength in union of the malar and maxillary bones shades off to the relatively thin canine fossae portion of the maxillae which at the medial rims form the pyriform aperture of the skeletal nasal opening. Thus the sturdy alveolar and palatal portions of the maxillary bones hang suspended by the thinner and weaker walls of the pneumatic chambers. Posteriorly this frailty is buttressed by the pterygoid bones and the vertical shafts of the palatal bones. Somewhat loosely fastened to the nasal aperture of the maxillary sinuses are the inferior conchal bones.

Jutting from the apex of this central facial pyramid in a position of unwarranted challenge is the quadrilateral or septal cartilage capped by the paired upper and lower lateral cartilages. They together with the vomer bone and the middle plate of the ethmoid are perched precariously atop the superior ridge and anterior nasal spine of the palatal maxillae. And thus is formed the nasal septum—that inquisitive structure so prone to intrusion and trauma.

Hanging from the skull base and the lower mandibular margin are the hyoid bone and the laryngeal complex. Their taut suspension between the mandibular symphysis and the anterior brim of the thoracic inlet is essential in the mechanics of an open airway. While normal

tonus is present in the strap and suprahyoid muscles, the laryngeal aperture cannot occlude against the anterior vertebral surface regardless of body position. Since the larynx and the hyoid are protected by retrocession and a high degree of mobility they are not frequently injured.

Immediate Post-Injury Problems

Fracture of these facial skeletal components may be single and simple or quite complex. In assessing the injury, the whole patient should get primary consideration. The airway is the first vital concern. The unconscious patient with inadequate reflexes will aspirate the blood and secretions pouring backward into his pharynx. A face down position will prevent this to large degree.

Fracture-recession of the mandible allows the tongue, hyoid and larynx to drop back and close the laryngopharynx. Traction on the tongue can correct this and can be maintained manually, by safety pin, or by an airway when available. The face down and sideward position helps.

Fracture of the hyoid bone and/or thyroid and cricoid cartilages is not relieved by any of the above and requires a prompt tracheotomy if the patient is to survive.

For the severely injured person the first post-injury week revolves to a great extent around airway considerations. When a state of profound unconsciousness continues, the patient's pulmonary drainage is confounded. This is often compounded by aspiration and partially obstructed respiration. Where mandibular and maxillary injury is present, fixation of the bones in firm occlusion must be contemplated. This creates anesthetic difficulties in multiple stage repairs. The impaired respiration of jaw occlusion and nasal airway trauma creates restlessness and anxiety. Sedatives and opiates speed a malicious sequence by diminishing reflexive protections. Procedural uncertainty in these circumstances should be resolved in favor of a tracheotomy. Pulmonary drainage as well as an airway are thus assured. Brain injury if present is not compounded by hypoxia. The patient rests well. Anesthetic procedure is no longer a problem.

In ordinary maxillary or central facial third injuries these considerations do not apply and tracheotomy is not usually necessary.

Immediate blood loss from external laceration and from mucosal surfaces may seem alarming, but it actually is rarely serious. Vessel

retraction in the soft tissues of the face is usually prompt and a compression dressing is then adequate. Occasionally a neck vein is less amenable to compression bandaging and has to be controlled manually until tied. Bleeding from the mucosal surfaces rarely requires tamponade. The nasal mucosa swells rapidly and effectively controls its own bleeding. Compounding and contaminating the injury by stuffing gauze into the nose is usually undesirable unless a reasonable wait and blood replacement do not suffice. Early and adequate transfusion is the best solution to the problem of significant blood loss.

When the airway and blood volume are well controlled a pause allows the patient to stabilize and his visceral and neurological status to be determined. The face is the least important part of the severely injured person. The urge to repair it should be subordinated to the over-all problem. Repair should be coordinated with other necessary surgery.

When general circumstances make surgical delay advisable, facial soft tissue injury can be protected with a compression dressing for twenty-four hours. If longer delay is unavoidable the soft parts can sometimes be cleaned, trimmed, and repaired at bedside with the aid of local anesthesia. Access to the skeletal fragments through the lacerations is frequently important for direct wiring and ideal fixation. It is necessary on occasion to open repaired lacerations for this purpose. The greatest aid to ideal soft tissue approximation is perfect skeletal realignment. Debridement of facial wounds can be conservative but must be thorough as to depth. All surface tattooing should be removed. Suture materials of 6-0 and 5-0 gauge with comparable needles should not be exceeded.

Closure must be in layers with least tension exerted at the skin surface. Skin sutures should not be placed wide of the laceration margins. Adhesive supports can be applied additionally. Edema and serum pooling are prevented by elastic dressings—circumferential are best when possible. Sutures must be divided in forty-eight hours and removed in seventy-two hours. Adhesive bridging is applied for support at the time of suture division. Antibiotics and good facial blood supply reduce infection to a minimum as long as debridement is adequate and mucosal surfaces have been properly repaired.

Skeletal Repair

Visual, manual and X-ray examination will determine the best

program for the facial skeleton repair. The objectives are good nasal function, good dental occlusion, normal ocular fusion, and the best cosmetic result obtainable.

The Nose

The composite of bones and cartilage collectively termed "the nose" leads all skeletal parts in fracture frequency. The superior one-third to one-half of the projecting portion of the nose is formed by the frontal processes of the maxillae surmounted by the nasal bones which unite atop the middle ethmoidal plate of the bony septum. This complex may shatter in the manner of an eggshell as a result of central facial third impact. The characteristic front seat passenger smash into the dash board produces this injury. The frontal maxillary process if sufficiently sturdy may fracture at the infraorbital abutment with the malar bone and impact with the lacrimal bone into the ethmoid labyrinth.

The usual athletic injury fracture dislocates the nasal bones from on top the frontal maxillary processes. The latter may fracture from the main body of the maxillae as well. In either case the septal plate of the ethmoid is carried in the direction of displacement. This must be reckoned with in the course of reduction.

Injuries of the upper nasal segment are easy to diagnose and delineate by palpation and inspection. X-ray examination is much less informative though perhaps more impressive. Doubt whether fracture has occurred can be resolved by looking and feeling again in a few days when soft tissue swelling has subsided. This delay does not prejudice the final result.

Realignment of these fractures can be accomplished by intranasal and external manipulation and molding. General anesthesia is frequently desirable. Usually the fragments maintain reposition without splinting. An external molded dressing is sometimes useful to minimize excessive edema. The latter can result in slippage of fragments. In addition it can result in undesirable thickening due to organization of transudate. A modest intranasal support of vaseline gauze strip high in the fornix can be useful to prevent impacted fragments from falling back into the chamber. Intranasal packing stuffed into the nasal space to counter bleeding is a useless and harmful routine measure.

If comminution is extensive and manual elevation of fragments will not maintain position with these simple efforts, direct wiring

and pinning is necessary. Two 30 gauge steel wires threaded on straight needles are passed through the base of the bony nasal mass. Comminution makes this maneuver easy. The wires are threaded through molded lead plates and the latter are snugged to the nasal skeleton to support an agreeable contour. On occasion recession of the maxillary frontal processes in the medial infraorbital area requires direct wiring through incision or laceration. A Kirschner wire skewered through will sometimes accomplish the same end quite simply.

The lower half of the external nose is frequently injured without upper half fracture. The magnitude of this injury is often overlooked. Most of the distortion is intranasal. Externally there may be no obvious displacement—only swelling and tenderness. A palpating finger must always be run down the nasal dorsum. A soft point immediately caudal to the end of the nasal bones means that septal fracture and dislocation has occurred. Intranasal septal swelling will fill the nasal vestibules and air spaces. This is due to a ballooning hematoma between the septal flaps. An early intranasal open reduction of this injury is mandatory. Lack of diagnosis and neglect result in external nasal deformity and septal airway obstruction. Rhinoplastic surgery for neglected distortion of the upper nasal injuries is uniformly satisfactory. Rhinoplastic and septoplastic surgery for correction of lower half injury is always a compromise. Once the dorsal ridge hematomatous soft spot absorbs and organizes, the inspiratory vault of the nasal vestibule is forever lowered. Though the later plastic correction obliterates the saddle of the dorsum and narrows the accordioned septum it cannot restore the height of the intranasal fornix. Diagnostic X-ray is useless in this injury. The keys to diagnosis are the soft spot in the lower half of the nasal ridge into which the palpating finger falls as it slides down the nasal dorsum and the complete obliteration of the nasal airway by the hematoma between the septal flaps.

The Mandible

The mandible may fracture in its vertical, its horizontal, or its symphysis segments. Multiple fractures are common. Thus the distortion of a side blow can fracture the impact point on the horizontal ramus and the opposite vertical ramus at the thin condylar neck. Direct impact can fracture the symphysis and one or both condylar necks. Fracture through the tooth-bearing portion is usually compounded into the mouth along the line of a tooth or through the tight mucoperiosteum of the edentulous jaw. The disposition of fractured

fragments is governed by the direction of impact and the pull of attachment of the masseter, temporal, and internal and external pterygoid muscles.

Pain, swelling, malocclusion, and disturbance of articulation suggest the diagnosis of mandibular fracture. Visualization and palpation of intraoral compounding, hematoma, and crepitus lend confirmation as do X-ray studies.

The preferable method of reduction and fixation of a mandibular fracture is governed by the presence or absence of teeth and the location of fractures. The objectives are good dental occlusion and articulation and firm bony union. Occlusion is obtained by direct simple loop or arch wiring. Traction through intermaxillary rubber bands or to external head cap appliance may be useful in reduction. The edentulous mandible or maxillae or posterior vertical fragment poses a special problem, as does subcondylar or condylar neck fracture. Open reduction and direct wiring through external approach is effective in some circumstances.

There are limitless appliances and techniques for mandibular fractures of unusual type. Amidst all this maze of gear and method the novice can flounder in confusion. He frequently adds a few of his own screws and bolts to the Rube Goldberg devices until sanity and experience reorient him to the virtues of the simple and the direct.

The Maxillae

The toothbearing palatal segments of the maxillae suspended as they are by thin bony laminae from the complex of the middle facial third are frequently broken free. The impacting force resulting in a floating palate can, by posterior displacement, fracture the vertical plates of the pterygoid and palatal bones. By locking posteriorly these bones may prevent the forward reposition of the entire palatal complex. Traction over a Balkan frame is occasionally necessary to bring the palate forward. Any and all efforts are warranted because the occlusal disability and disfigurement of retrocession are severe and permanent. The palate may displace as a unit or it may fragment. In any case realignment of all fragments with the opposite mandibular segments and fixation with intermaxillary wiring results in good functional and cosmetic healing.

The pyramid in the center of the middle facial third is comprised of the maxillae, the nasal, lacrimal, and ethmoidal bones and the in-

tranasal vomerine and inferior conchal components. Straight, forceful projection of the face into an unyielding receiver may impact the nasomaxillary mass without free fracture of the palatal segment or both may take part in the disruption. A combination of intermaxillary fixation and naso-maxillary realignment and fixation by the methods discussed under the nasal heading give good restoration.

It is important to disimpact the nasomaxillary mass at the first opportunity. Early fusion occurs. A bulging of the ethmoidal labyrinth and retrocession of this central mass is impossible to correct by later plastic repair. Manual realignment must be supplemented with elastic-head cap or weight and frame traction if necessary. Bone reunion occurs in a matter of weeks due to the thin plates, extensive periosteal surfaces and rich blood supply.

The Malar Bones

Laterally the malar bones form the buttress and contour of the cheeks. The human has a marvelously rapid protective reflex that turns the head at the instant of impact. The brunt of many blows is borne by the malar bones. Their attachment points . . . frontal, temporal, and infraorbital—and alveolar-maxillary . . . are weaker than the body of the bones. Only occasionally is the bone fragmented. Displacement, however, can be gross because the large underlying maxillary sinus space is no support. Rapid swelling tends to obscure the true extent of the cave-in. The line of fracture in the orbital floor tears the periorbita. Hematoma supports the globe at normal level for a week or two but when it resorbs, the globe drops and this together with displacement of the bony attachment of the inferior oblique muscle can result in diplopia of very disabling character. This same hematoma dissects under the bulbar conjunctiva to the limbus. This subconjunctival hemorrhage should warn the examiner that here at least is one swollen and ecchymotic eye that should not be made the butt of door knob jokes. The humor incident to a "black eye" loses much of its flavor when the patient returns in two weeks with a flattened face and diplopia.

A chin-nose position film as of the maxillary sinuses is quite diagnostic of malar fracture. The presence or absence of displacement should not be determined finally by the film, however. Its angle may not define significant malposition. The palpating thumb placed along the

infraorbital edge may reveal a step-down that is not well shown on the film.

Since the weak point of fracture on the infraorbital rim is at the infraorbital foramen, anesthesia of this sensory nerve is usual with malar displacement. Hence numbness of the upper lip and nasal ala on the side of the injury is an important diagnostic sign. So also is the presence of blood in the maxillary sinus due to tear of the mucoperiosteum.

Reposition of the malar bone can be accomplished in several ways. There is no best way for all fractures. The objective of reversing the injury force to realign the fragments demands familiarity with a number of approaches.

A lateral blow can be reversed through a temporal hair line and temporal fascia incision with the elevator placed beneath the malar arch. Inferior displacement of the body can sometimes be corrected by manipulation with a bone hook externally or elevation through the buccal mucosa intraorally. Posterior impaction of a substantial fragment of the infraorbital rim may require direct exposure through a well placed infraorbital incision and retrieve of the fragment with a fine hook. This exposure allows direct wiring across the fracture line. As with nasomaxillary fragmentation this is accomplished with a belt-drive drill, fine drill points and fine steel wire loops.

It is generally inadvisable to attempt manipulation of the malar bone with towel clips or by entering the maxillary sinus through the canine fossa. The former method endangers facial nerve filaments when the tenaculum slips and the maxillary opening requires sacrifice of bone in opening the sinus that should be present to support the repositioned malar.

Occasionally the bone will not hold in anatomic reposition. Direct wiring to the frontal abutment through a lateral brow incision with or without infraorbital wiring is then useful. On rare occasion it can be supplemented with binder traction from a screw inserted in the body of the bone to a head cap appliance. An impaling Kirschner wire carried across to firm supportive bone of the opposite side is sometimes a simple and useful fixation method. Methods of support working from inside the sinus such as balloons, etc. are generally inferior to direct fixation of the bone fragments.

Solid healing in malposition is frequently best corrected by osteotomy, re-fracture along the four main fracture lines and reclamation

of the bone itself for replacement and direct fixation. The results are generally superior to those obtained with implantation of iliac bone or diced cartilage.

Complex Fractures

The more challenging injuries of the facial skeleton are those that combine injury to all or most of the component bones. As with the reduction of fractions to the lowest common denominator, so also is the most complex facial fracture reducible to individual components as above. Corrected in good sequence by these methods with the accent on direct visualization of fracture lines, anatomic realignment and simple fixation, the most complicated injury is usually amenable to functional and cosmetic restoration.

The Larynx

When the larynx is fractured the patient's survival usually hinges on a reasonably prompt tracheotomy. Some patients do survive without tracheotomy or recognition of the true nature of their injury. This is only because of their great fortune in a less severe injury.

The respiratory embarassment and hoarseness as well as the contusion and tenderness in the anterior neck are ample evidence of traumatic intralaryngeal mischief. This is not an indication for casual investigation even though tracheotomy is not essential. Early correction of laryngeal damage is vital to the best voice result. The least one can hope for is dislocation of the arytenoid cartilage from the cricoid. Since the vocal cord is attached to the arytenoid, reduction of the dislocation can restore some motion if organization in malposition is not permitted. On the other hand fracture of the thyroid cartilage tears the attached vocal soft parts and may even compound through them into the airway. Moulding the cartilages into anatomic position can be accomplished by insertion of an endoscopic tube through the larynx. More often than not this maneuver must be guided by exposing the external aspect of the larynx and verifying the realigning of fragments directly. A collar incision and reflection of overlying soft tissues provides this direct view. An indwelling sponge mold placed in the laryngeal lumen to encourage the resorption of hematoma and adherance of perichondrial flaps can be important in preventing intraluminal stenosis.

Delay in all of the above is disastrous. Once the soft tissues of the vocal apparatus have foreshortened and organized they are forever lost for normal vocal function. Late coring and grafting provide a poor substitute for the restoration of early reduction.

Editorial

Conservation

Today we face a shortage of trained people in many areas. The shortage is acute in the technical and scientific fields, including the basic medical sciences. This situation has not arisen because we are training fewer people in science; it is due primarily to the increasing demand for scientists and technicians. It is significant, however, that in spite of the increasing number of graduates in science in this country since 1900, the percentage of college students majoring in science has decreased steadily.

How are the demands for more scientists and technicians to be met? Do we have capable high school graduates who are not continuing their training? Are we wasting our most precious natural resource; intellectual ability? These questions are discussed in a recent volume, *Encouraging Scientific Talent,* by CHARLES C. COLE, JR., *Assistant Dean* of Columbia College, Columbia University. With the huge increase in college enrollment expected during the next decade, some have expressed the fear that an overproduction of trained personnel will result. There appears to be little basis for this fear as far as scientific manpower is concerned. The demand is expected to outstrip the supply for many years to come.

Do we have the potential to supply these needs if we stop wasting our intellectual resources? Studies at the national level indicate that one-half of the high school graduates in the top 20 per cent in ability are continuing their education. The picture in our own state is not markedly different. Many of these young people of ability are not interested in continuing their formal education but others would attend college if they could. Prof. Ralph Birdie's recent study of the situation in Minnesota revealed that at least one-half of our high-ability high school youth who were not planning to attend college would have gone if they had had enough money. These are the people we must salvage.

It would be difficult to estimate the returns to society that would result from college and professional training of these gifted young people who wish to continue their education but cannot for financial reasons. Other young people of ability, who now express no interest

in attending college, might develop such an interest if college attendance could be accomplished without severe strain on the family finances. The few dollars that it would cost to provide scholarships for these people, would be returned manyfold in increased productivity. Can we afford to waste our most valuable natural resource?

Postgraduate Education

Electrocardiography for General Physicians

The University of Minnesota announces a continuation course, An Introduction to Electrocardiography for General Physicians, which will be held at the Center for Continuation Study on the University Campus from May 6 to 10, 1957. This course is intended primarily for physicians with little or no previous experience in electrocardiographic interpretation. Basic principles, variations in normal patterns, and frequently observed abnormalities will be stressed. Registrants will have an opportunity to interpret more than 200 electrocardiograms under supervision of qualified instructors. Guest lecturer will be DR. MAURICE SOKOLOW, *Associate Professor,* Department of Medicine, University of California Medical School, San Francisco. The remainder of the faculty will include members of the faculties of the University of Minnesota Medical School and the Mayo Foundation.

Proctology for General Physicians

The University of Minnesota will present a continuation course in Proctology for General Physicians at the Center for Continuation Study from May 13 to 17, 1957. Management of commonly-met proctologic problems will be stressed, and diagnostic and surgical techniques will be demonstrated. Guest speaker will be DR. FRED B. CAMPBELL, Kansas City, Missouri. The faculty for the course will include members of the faculties of the University of Minnesota Medical School and the Mayo Foundation. The course will be presented under the direction of DR. WALTER A. FANSLER, *Professor and Director,* Division of Proctology.

Notice

All continuation courses presented by the University of Minnesota are approved for formal postgraduate credit by the American Academy of General Practice. Attendance certificates will be furnished on request.

Further information concerning the above programs or others to be presented may be obtained by writing to Dr. Robert B. Howard, 1342 Mayo Memorial, University of Minnesota, Minneapolis 14.

WEEKLY CONFERENCES OF GENERAL INTEREST

Physicians Welcome

Monday,	9:00 to 10:50 A.M.	OBSTETRICS AND GYNECOLOGY Old Nursery, Station 57 University Hospitals
	12:30 to 1:30 P.M.	PHYSIOLOGY- PHYSIOLOGICAL CHEMISTRY 214 Millard Hall
	4:00 to 6:00 P.M.	ANESTHESIOLOGY Classroom 100 Mayo Memorial
Tuesday,	12:30 to 1:20 P.M.	PATHOLOGY 104 Jackson Hall
Friday,	7:45 to 9:00 A.M.	PEDIATRICS McQuarrie Pediatric Library, 1450 Mayo Memorial
	8:00 to 10:00 A.M.	NEUROLOGY Station 50, University Hospitals
	9:00 to 10:00 A.M.	MEDICINE Todd Amphitheater, University Hospitals
	1:30 to 2:30 P.M.	DERMATOLOGY Eustis Amphitheater, University Hospitals
Saturday,	7:45 to 9:00 A.M.	ORTHOPEDICS Powell Hall Amphitheater
	9:15 to 11:30 A.M.	SURGERY Todd Amphitheater, University Hospitals

For detailed information concerning all conferences, seminars and ward rounds at University Hospitals, Ancker Hospital, Minneapolis General Hospital and the Minneapolis Veterans Administration Hospital, write to the Editor of the BULLETIN, 1342 Mayo Memorial, University of Minnesota, Minneapolis 14.