Bulletin of the

University of Minnesota Hospitals
and
Minnesota Medical Foundation

Megaloblastic Anemia

Volume XXI | Friday, January 27, 1950 | Number 14

BULLETIN OF THE
UNIVERSITY OF MINNESOTA HOSPITALS
and
MINNESOTA MEDICAL FOUNDATION

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Published weekly during the school year, October to June, inclusive.
Annual Subscription Rate - $3.00.

Address communications to: Staff Bulletin, 332M University of Minnesota Hospitals, Minneapolis 14, Minn.

I. EXPERIMENTAL PRODUCTION OF MEGALOBLASTIC ANEMIA IN RELATION TO MEGALOBLASTIC ANEMIA IN INFANTS

Charles D. May
Edward N. Nelson
Robert J. Salmon
Charles U. Lowe
Roger I. Lienke
R. Dorothy Sundberg

Introductory

The importance of megaloblastic anemia in infants was not generally appreciated until Zuelzer and Ogden's classic description of the syndrome in 1946.[1] This may be attributed to an almost universal neglect to examine the bone marrow in infants with anemia during life. Fortunately the technique of aspiration of sternal marrow during life was introduced into this clinic soon after its development.[2] The megaloblastic character of the marrow in certain infants with anemia had been recognized by Reiff and Sundberg since as early as 1943.[3] Consequently, Aldrich and Nelson were able to report a group of infants with megaloblastic anemia in 1947,[3a] not long after Zuelzer's comprehensive and definitive description of the syndrome. Particular tribute must be paid to Dr. Robert Aldrich, who while Pediatric Resident of the University Hospitals, collected clinical data on the patients being recognized by Sundberg and Nelson and shared in observations which ultimately contributed to the conception guiding the investigations summarized in this report.

Once the surprisingly frequent occurrence of a megaloblastic type of anemia in infants was thus firmly established, attention was naturally directed to its pathogenesis. The megaloblastic type of marrow had come to signify deficiency of certain materials in liver which are effective in pernicious anemia. Now we know the nature of two of these factors, vitamin B_{12} and pteroylglutamic acid (PGA). But pernicious anemia as known in adults is extremely rare in children. Furthermore, it was clear that the megaloblastic anemia in infants described by Zuelzer and also recognized in this clinic was not to be confused with pernicious anemia, because a single effective treatment resulted in complete and lasting cure. The pertinent question was then, how did infants so often become deficient in these essential hematopoietic factors?

The circumstances which might lead to a deficiency of these factors during infancy are outlined in Table I.

Table I

DEFICIENCY OF VITAMIN B_{12} AND PGA MIGHT RESULT FROM:

Deficient diet.
Altered bacterial flora in intestine.
Impaired gastric function.
Impaired intestinal absorption.
Defective intermediary metabolism.
Unusual requirements
- Infection, rapid growth.
- Imbalance or loss of "Sparing effects".
- Inhibitors or antagonists.
- Inadequate stores from mother.

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ACKNOWLEDGMENTS

We are appreciative of the interest of Dr. Irvine McQuarrie who facilitated this investigation in many ways.

This study would not have been possible without the faithful technical assistance of Drusilla Deis, Gertrude Honig, Gale Slater, Frances Acko and Jay Little.

The generous financial support of Wyeth, Inc. and M and R Dietetic Laboratories is gratefully acknowledged.

It is immediately apparent that no one mechanism is likely to account for all instances of megaloblastic anemia in infants. Indeed, one would anticipate the same variety as occurs in adults where this type of marrow occurs in pernicious anemia, liver disease, sprue, pregnancy, and in simple malnutrition.

The essential clinical features of infants suffering from megaloblastic anemia were remarkably simple and uniform. The majority, after a normal birth and neonatal period, were weaned after a few days to a few weeks and reared on artificial cow milk feedings. No evidence of ill health appeared for a few months when anorexia became a troublesome complaint. Pallor was noted most frequently by 5-9 months of age. The course was one of increasing anorexia and pallor until a final phase of the illness when a precipitous decline began and soon the infants were desperately ill with profound anemia. Only an occasional infant passed into the second year of life without developing this sort of crisis. Zuelzer was impressed with the frequency of infections during the infants course, whereas Aldrich and Nelson felt that infection was usually only a terminal event in their patients. The infants did not appear to have had any antecedent abnormality in the gastro-intestinal tract, though diarrhea was a frequent complication and achlorhydria was present in the final phase of their illness. Although functional achlorhydria is common in the first 6 months of life, real achylia gastrica is rare.[4] Data concerning sex, maternal history or any other disease were not generally helpful. (A description of the hematological findings is given later in this report.)

Naturally the diets of these infants were scrutinized and at first they seemed most heterogeneous and to be the types which regularly permitted infants to thrive. One series of 25 infants who were fed almost exclusively at the breast for their entire lives was collected during World War II in Naples, Italy.[5] The American reports were made up mostly of infants fed ordinary pasteurized cow milk, evaporated cow or goat milk, and proprietary cow milk infant foods. Aldrich and Nelson made the observation that the diet of all of the patients in their series was the same proprietary infant food. In a subsequent paper Zuelzer[6] noted that 70% of his patients had been reared on either human milk or proprietary infant foods of the same percentage composition as human milk. Human milk and those artificial foods most nearly resembling it contain 1.5% protein, while evaporated and whole cow milk formulae as generally prescribed by pediatricians contain about 2.6% protein. This difference led to the supposition that the lower protein intake might predispose infants to megaloblastic anemia. However, there are many conditions in infancy which result in lowered intakes of protein and yet are rarely complicated by megaloblastic anemia.

Furthermore, it has not been possible to produce megaloblastic anemia in experimental animals by feeding diets inadequate only in protein. Wills[7] and Day[8] produced macrocytic anemia in monkeys by means of diets which were low in animal protein but deficient in other essential nutrients as well. The only other means of producing megaloblastic anemia in experimental animals has been to use vitamin free protein in the diets and a PGA antagonist such as aminopterin.[9] Diets virtually devoid of protein but supplemented with all known vitamins result only in a moderate anemia which is neither macrocytic nor megaloblastic.[10] Therefore, one might expect that lower intake of protein, if of any significance in connection with megaloblastic anemia, would be important chiefly in terms of vitamins intimately associated with the protein.

An interesting observation regarding the diets of infants developing megaloblastic anemia, stressed by Aldrich and Nelson and commented upon by Zuelzer was the frequent history of an inadequate intake of vitamin C (at least 50% of the reported cases) and the unusually high incidence of 25% with clinical signs of scurvy. There were several reasons which led us to seize upon this observation as having some importance as a factor in the pathogenesis of this megaloblastic anemia:

(1) Megaloblastic anemia has been reported frequently as a complication of scurvy.[11a,b,c]

(2) Patients with pernicious anemia have been encountered who were said to be refractory to liver extract until ascorbic acid was administered.[12]

(3) Either PGA or ascorbic acid will relieve the tyrosyluria induced in scorbutic guinea pigs by feeding excessive tyrosine.[13]

(4) Megaloblastic anemia had not been produced by feeding a wide variety of deficient diets to species which are able to synthesize ascorbic acid.[10]

(5) Wills[7] and Day[8] had produced macrocytic anemia in monkeys with diets devoid of animal protein or containing vitamin free casein but the animals were protected from anemia if milk or ordinary casein and ascorbic acid were included in the diets.

Therefore, infants fed cow milk formulae with adequate ascorbic acid ought not develop megaloblastic anemia unless some interference with intake or utilization was present. It has already been stated that such conditioning factors were uncommon but the frequency of deficiency of vitamin C was impressive.

Plan of Experiments

The objective was to feed monkeys (a species susceptible to deficiency of vitamin C and known to be capable of developing megaloblastic anemia (Wills)) the type of milk diets which infants with megaloblastic anemia had consumed, with and without vitamin C. Monkeys varying in age from newly born to nearly mature were employed to include the demands of growth. The composition of anthropoid milk is more nearly that of human milk than any other species[14] making nutritional requirements of the two species more comparable.

The milk diets employed and some data on their composition are given in Table II.

Table II

MEGALOBLASTIC ANEMIA
EXPERIMENTAL DIETS

No.	Type	Composition (Per 100 cc as fed) Protein (gms)	PGA (microgms)*	Vit.C (mgs.)**
1.	Human Milk Fresh unpasteurized	1.4	.3	5.0 0.2 (boiled)
2.	Infant Food A	1.3	.3	0.2
2a.	Infant Food A + Casec	3.3		
3.	Infant Food C	1.5	.3	0.3
3a.	Infant Food C + Casec	3.3		
4.	Dried Cow Milk Formula	1.6	.2	0.8 0.6 (boiled)
5.	Evaporated Cow Milk Formula	2.6	.3	0.5 0.5 (boiled)
6.	Evaporated Goat Milk Formula	2.6	.2	0.7 (boiled)

NOTE: Other Vitamins present in 100 cc: Vitamin A 800 I.U., vitamin D 50 I.U., Thiamine .07 mg., Riboflavin 0.1 mg., Nicotinic Acid 0.5 mg plus any other vitamins in the milk.

* PGA determined by microbio assay.

** Vitamin C determined by chemical analysis.

It will be seen that different quantitative levels of protein intake were utilized and the effect of adding more protein to the lower protein diets was tested. The milks were also selected to bring out any qualitative differences due to the species from which it was derived or methods of handling the milk in the process of manufacture.

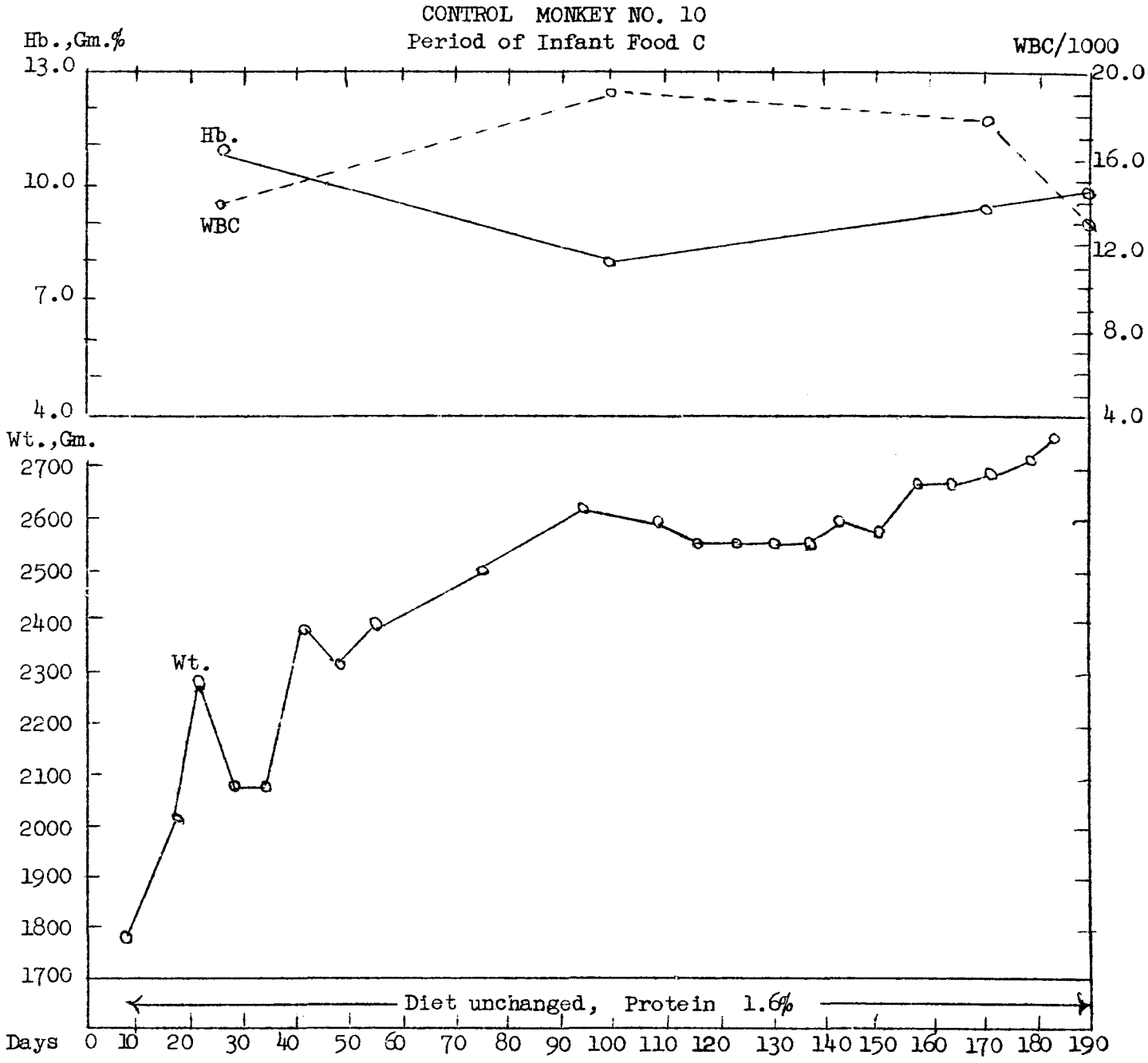
Results

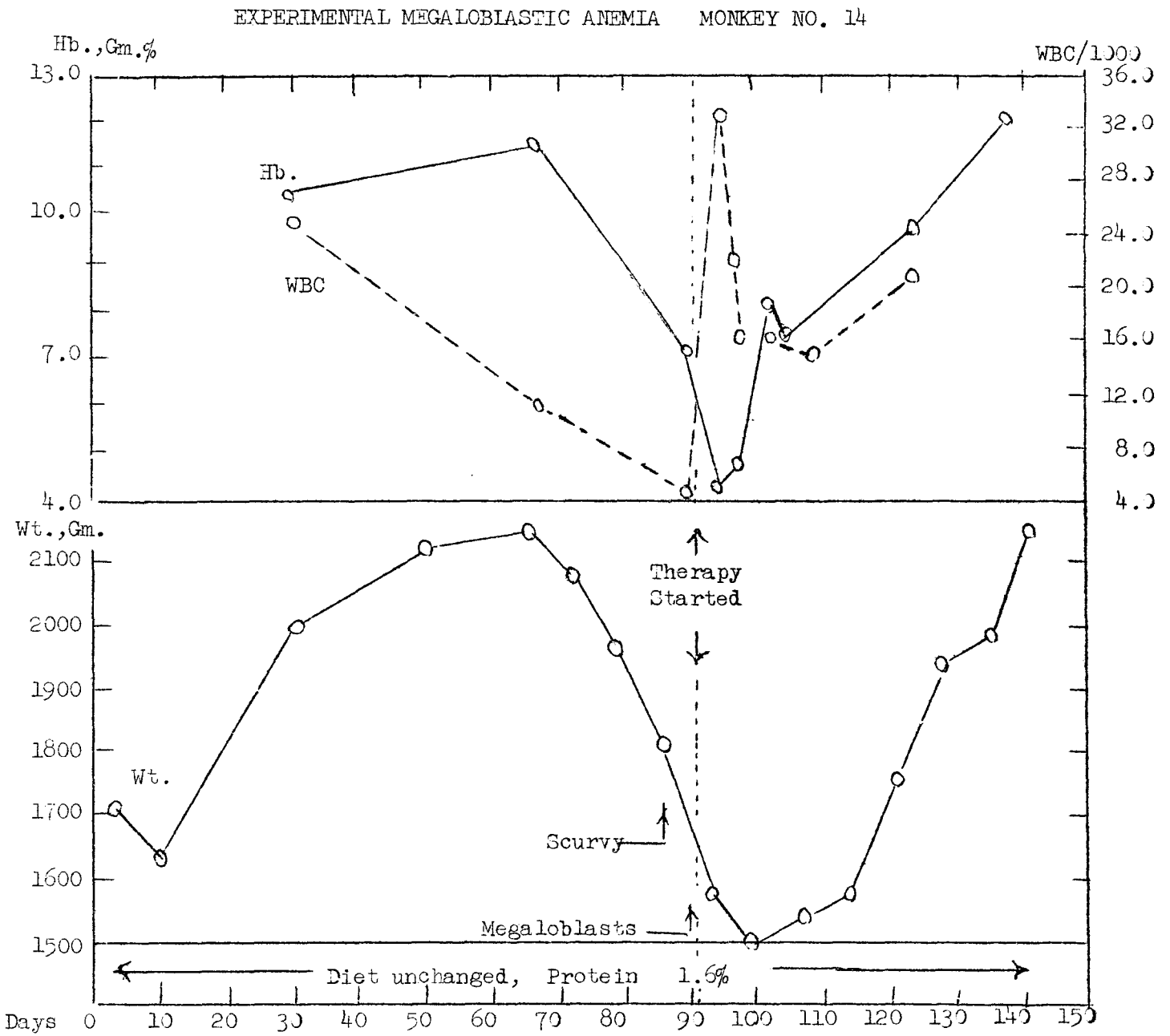
The results of feeding these diets may be easily gathered by studying the accompanying graphs of representative experiments (Charts of Monkeys, No. 10 and No. 14). Changes in weight, hemoglobin, and white blood cell counts are depicted. The character of the bone marrow in the anemic phase is indicated. A summary of all the animals is given in Table III.

Table III

SUMMARY OF ANIMAL EXPERIMENTS

Diet No.	Monkey No.	Approx. Days before appearance		Remarks
		Scurvy	Meg.Anem.	
1+Vit.C	17A (control)	No scurvy	or anemia	in 90 days.
1	11A	73	102	PGA+C Effective.
2+Vit.C	4B (control)	No scurvy	or anemia	in 135 days.
2	1	50	60	Died on 63rd day
2	2	130	135	Died on 139th day
2	3	120	130	Died on 130th day
2	6	70	74	Died on 74th day
2+5 microgm PGA daily	14A	86	90	B12 no effect in 40 hours PGA Effective
2A	8	86	93	Vit. C 10 days before death on 103rd day.
3+Vit.C	10 (control)	No scurvy	or anemia	in 220 days
3	9A	120	123	Recovered with Vit. C alone
3	9B	90	107	Sacrificed 107th day
3+5 microgm PGA daily	15A	110	108	B_{12} no effect 54 hours PGA Conjugate Effective
3A	13A	73	78	PGA Effective
4+Vit.C	4C (control)	No scurvy	or anemia	in 165 days
4+Vit.C	7 (control)	No scurvy	or anemia	in 312 days
4	5	302	308	Sacrificed 312th day
4+5 mg. PGA Daily	14B	105	Never	PGA prevented meg. marrow Sacrificed on 120th day
5+Vit.C	4A (control)	No scurvy	or anemia	in 285 days
5	12A	131	160	B_{12} + C Effective
6+Vit.C	11B (control)	No scurvy	or anemia	in 75 days
6	17B	78	90	No food and aureomycin during Trial of B_{12}+ C - Ineffective.


CONTROL MONKEY NO. 10
Period of Infant Food C
Hb.,Gm.%
WBC/1000
13.0
10.0
7.0
4.0
20.0
16.0
12.0
8.0
4.0
Hb.
WBC
Wt.,Gm.
2700
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
Wt.
Diet unchanged, Protein 1.6%
Days
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190


EXPERIMENTAL MEGALOBLASTIC ANEMIA MONKEY NO. 14
Hb., Gm.%
WBC/1000
13.0
10.0
7.0
4.0
36.0
32.0
28.0
24.0
20.0
16.0
12.0
8.0
4.0
Hb.
WBC
Wt., Gm.
2100
2000
1900
1800
1700
1600
1500
Wt.
Therapy Started
Scurvy
Megaloblasts
Diet unchanged, Protein 1.6%
Days 0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150

All of the diets, when fed ad libitum, along with 50 mg. of vitamin C daily, enabled the monkeys to thrive and in no instance did megaloblastic anemia develop during control periods of 5 months to one and a half years duration.

Megaloblastic anemia developed in every monkey, no matter which of the diets was fed ad libitum, if vitamin C was not given. They ate heartily until symptoms of scurvy appeared.

A very uniform sequence of symptoms appeared in the monkeys developing megaloblastic anemia. For the first two to three months on one of the experimental diets devoid of ascorbic acid a monkey would gain weight, behave normally, and reveal no anemia or tendency to a megaloblastic type of marrow. The first signs of ill health were gradual loss of weight and a lessening of appetite. Changes in the bones of the wrist characteristic of scurvy have been found at this time, but obvious signs of scurvy such as periorbital hemorrhages, gingival hemorrhage, beading of the costochondral functions, pain and swelling in the extremities did not usually appear until several weeks later. The hemoglobin and marrow sometimes remained normal for about a week after obvious scurvy. Once scurvy became evident a series of dramatic changes began. The anorexia became profound and the monkey lost all his usual spirit, alertness, and activity, tending to sit hunched in a corner of the cage. Leucopenia was a common finding at this stage. Diarrhea invariably developed, rapidly becoming severe. Often the feces became paler, fatty, and foul, reminiscent of the stools in sprue. Mucus was rare; fresh blood was uncommon and appeared to be because of the scurvy. It may be mentioned in passing that the stools became normal promptly after appropriate vitamin therapy, but antibiotics had little if any effect. The gums became necrotic and fetid. The fur lost its lustre and was sometimes shed in large amounts. A number of the animals became so desperately ill that supportive treatment, such as gavaging, parenteral fluids, and antibiotics, was required to prolong their lives until a specific type of therapy could be tested. In this terminal phase, pallor and anemia developed rapidly and the marrow would frequently change from normoblastic to megaloblastic in a few days. As soon as an appropriate specific vitamin therapy was instituted all of these symptoms and findings were promptly relieved and a surprisingly rapid recovery to good health ensued, even though the experimental diet was not changed. The changes in the blood and marrow are described in the section of this report devoted to hematology. Megaloblastic anemia was thus produced 14 times; in every monkey fed any of the experimental diets without ascorbic acid. No evidence of infection of any sort preceded the onset of the megaloblastic anemia. Tuberculin tests were repeatedly negative. The anemia developed as quickly in the nearly mature monkey as it did in the newborn, some of which were reared artificially from the moment they were born. Macaccus Rhesus and Cynamologous species of monkeys behaved identically. Both sexes were equally susceptible and needless to say, the maternal diets varied, some being born in captivity where the maternal diets seemed adequate. Evidence of antecedent gastric or intestinal disorders was present in only one animal who had chronic diarrhea. Gastric analyses before the experiments showed free acid to be present in fasting secretion in all but one monkey after stimulation with histamine.

As soon as it was found that megaloblastic anemia could be produced, an attempt was made to gather data concerning the effect of the implicated vitamins B_{12} and PGA, as well as vitamin C. These were tested alone and in combination, always while the animal remained on the diet being consumed when the anemia developed and in one instance (#17) without any food at all. The effects of these substances are discussed in the section on hematology.

The data on PGA in the livers of experimental animals are given in Table IV.

Table IV

EXPERIMENTAL MEGALOBLASTIC ANEMIA
TOTAL PGA IN EXCRETA AND LIVERS

Urine		
Controls.....	.06-.55	per 24 hrs.
Anemic.....	.04-.42	per 24 hrs.
Feces		
Controls.....	18-56	per 24 hrs.
Anemic.....	10-50	per 24 hrs.
Livers		
Control.....	1.42	per gm.
Sick.....	.67-.80	per gm.
Anemic (6) Av..	.18 (.04-.48)	per gm.

It may be seen these data are in keeping with the development of megaloblastic anemia and its cure by PGA. The urinary excretion was disappointing. The fecal excretion invites speculation.

Recapitulation of Animal Experiments Leading to Megaloblastic Anemia

1. When Vit. C provided adequately diets tested did not lead to megaloblastic anemia.
2. If Vit. C inadequate, same diets all resulted in megaloblastic anemia.
3. Age, sex, maternal diet, species appeared to have no influence.
4. No antecedent abnormalities in gastric and intestinal function.
5. Diets with proteins differing qualitatively and quantitatively behaved identically.
6. Megaloblastic anemia cured by crystalline vitamins while continuing same diet.
7. Infection did not play an etiologic role.
8. Megaloblastosis of the marrow is eliminated by PGA and is prevented by regular administration of PGA, even in the absence of vitamin C.
9. With B_{12} alone the megaloblastic marrow is not significantly altered.
10. Vitamin C given alone may permit complete recovery.

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Hematology of Megaloblastic Marrow in the Human Compared with the Experimentally Produced Megaloblastic Marrow in the Monkey.

The aspiration biopsy of bone marrow provided a great stimulus to the study of megaloblastic anemias. Positive diagnosis of megaloblastic anemia in the human has been possible on the basis of study of the marrow in early stages of relapse when, paradoxically, there may be no remarkable anemia. Although most study has been directed at the megaloblasts and the giant "pernicious anemia neutrophils" of pernicious anemia, the presence of similar developing erythrocytes and neutrophils in conditions such as sprue, carcinoma of the stomach, pregnancy, and megaloblastic anemia in infancy as well as in other rarer conditions has been recognized. Of primary importance from the standpoint of morphologic hematology is the fact that consistent means have not been

apparent for distinguishing the developmental abnormalities in the cells of these conditions from the abnormalities seen in pernicious anemia in various degrees of relapse or remission.

Morphologists have in recent years focused their hopes on the experimental production of megaloblastic anemia, but the possibility of actually producing changes in the marrow sufficiently similar to those seen in pernicious anemia to warrant their use in extensive study of the changes seen in the erythrocytic and granulocytic cell series has seemed remote. Consequently, many attempts at evaluating the nature of the series of changes which occur in the marrow in early relapse and in various phases of remission in pernicious anemia have been made. We have learned, by means of serial aspiration biopsies, to expect a variety of changes in uncomplicated pernicious anemia in various degrees of relapse, and we have learned to recognize many of the changes which follow specific therapy. However, the true nature of the changes is still a matter of controversy because critical stages of transition are lacking.

Now, because of the efforts described in this report, it is possible to study the hematologic changes in megaloblastic anemia of the monkey. The marrow abnormalities, perhaps most similar in their development and regression to those seen in the megaloblastic anemia of infancy, fulfill all rigid criteria necessary for complete acceptance. The abnormalities seem as nearly similar to those seen in the human megaloblastic anemias as one could expect in an experimental animal. The primary important differences apparent at present are that:

(1) The normal neutrophil of the monkey often goes through a ring phase in its development and the segmented form may have many lobes.[1] Although because of this hyperlobulation one might expect some difficulty in identifying the abnormal neutrophils associated with the production of megaloblasts, the abnormal cells show many differences in morphology which often make them more easily identifiable than are the early megaloblasts.

(2) The degree of change produced is often virtually lethal, and the percentage of promegaloblasts and basophilic megaloblasts may be as high as that in pernicious anemia in extreme relapse.

The megaloblasts of the human and of the monkey are, of course, not identical cells. Fine morphologic differences exist, but if one can accept, as a basis of comparison, the profound changes in cells of the neutrophilic series as one criteria of degree of change of the marrow in the experimental megaloblastic anemia, then one might postulate that the finer morphologic changes could be the result of difference in species rather than of difference in cell type.

The megaloblasts of the human are recognizable on the basis of the following morphologic criteria:

(1) Cell size is variable, but megaloblasts are generally larger than normoblasts.

(2) Megaloblasts go through consecutive stages of development classified as pro-, basophilic, polychromatic, and orthochromatic as do normoblasts, but there is less tendency toward reduction in cell size in cells of the megaloblastic series, and hemoglobin can be seen in cells of this series while the nucleus retains the pattern of an immature cell.

(3) Megaloblasts generally have a relatively more abundant cytoplasm than do normoblasts, and often the cytoplasm is more heterogeneous in appearance.

(4) The nuclear pattern of the megaloblast remains delicate until the cell has attained its full complement of hemoglobin in many instances. The chromatin forms a relatively easily distinguishable "net"; the nuclear sap is easily seen through this net. As the cell matures, the strands of the net become coarser and they seem

more widely separated. This allows clear visualization of nuclear sap. Aggregation of chromatin occurs as the cell matures but the chromatin particles are small, and they tend to occur where one chromatin strand intersects another. The pattern often resembles that of a wide-meshed fish net. Nucleoli are variable in size, shape, and number. They frequently remain visible through the pro-, basophilic and polychromatic stages. Only rarely are they found in orthochromatic megaloblasts.

In contrast, the nucleus of the normoblast shows early aggregation of chromatin into relatively coarse masses. The nuclear sap is distinct but less prominent and less abundant than that of the megaloblast. The chromatin particles are distributed radially, and by the polychromatic stage in the development of normoblasts, the nucleus often resembles a spoked-wheel. It has been called the "Radkern" nucleus. Nucleoli vary in normoblasts as well as in megaloblasts, but they are generally not seen after the basophilic stage of development.

(5) The chromosomes of megaloblasts appear to be longer and thinner than those of normoblasts. Multipolar mitoses or various signs of abnormal division of nuclei are not unusual in megaloblasts whereas such abnormalities are extremely rare in normoblasts.

(6) Karyolysis is frequent in megaloblasts, but it is rarely, if ever, seen in normoblasts. Karyorrhexis is very common in megaloblasts. Although karyorrhexis does occur in normoblasts, it is considered one sign of pathologic regeneration of erythrocytes, and it is usually not conspicuous unless there is a defect in erythropoiesis. Multiple Jolly bodies, which result from karyorrhexis and further pyknosis of nuclear fragments, are commonly found in megaloblasts and in the macrocytes (or megalocytes) derived from megaloblasts. When the nucleus of a normoblast undergoes pyknosis, a single Jolly body may result. Although multiple Jolly bodies occur in very occasional orthochromatic normoblasts and in erythrocytes, they are present only when karyorrhexis has taken place. Basophilic stippling, another sign of pathologic regeneration, is common with megaloblastic regeneration of erythrocytes, but it is of much less distinctive value in comparative studies since it occurs with normoblastic regeneration of erythrocytes as well.

The preceding descriptions are presented for human material as a basis for an understanding of the changes seen in erythropoiesis in the monkeys which show various degrees of megaloblastic anemia. The megaloblasts of the monkeys show a similar morphologic and developmental pattern. The differences between the megaloblast of the monkey and of the human seem minimal. Although the importance of these differences may become apparent with future study, at present the variations seem no greater than those seen in the megaloblast of the human.

The "pernicious anemia neutrophil" seen in the blood in pernicious anemia and its precursors in the marrow often prove of great value in diagnosis. Since giant hypersegmented neutrophils occur in the blood in conditions not associated with megaloblastic erythropoiesis, there may be some difficulty in positive identification of a circulating cell of this type as a "pernicious anemia neutrophil." The precursors of the "pernicious anemia neutrophil" seen in the marrow, are, however, more easily identifiable. The features present in the development of the "pernicious anemia neutrophil" include the following:

(1) There is generally an increase in the size of the immature neutrophils. This may be apparent at the promyelocyte, myelocyte, or metamyelocyte stage. In some instances the leukoblasts and myeloblasts from which the immature neutrophils are formed may also be abnormally large cells.

(2) The nucleus fills a large part of the cell body and retains an immature and delicate nuclear pattern through the consecutive myelocytic stages. There is often evidence of beginning segmentation, manifested by contortion and bizarre nuclear shape, as early as the promyelocyte stage. Occasionally even leukoblasts show bizarre nuclear shape. Often there is some vacuolization of portions of the nucleus, and as a result of this the nuclear lobes seen in the mature cells may be connected to one another by several long delicate filaments of chromatin.

(3) Neutrophilic granules vary in size and staining reaction from one case to another. Generally the granules appear more acidophilic, more numerous, and more evenly distributed in the cytoplasm of the mature "pernicious anemia neutrophil" than do those of the normal neutrophil.

Similar changes in cells of the neutrophilic series occur in the marrows of monkeys with megaloblastic anemia. Often, in the material from monkeys, the changes in the neutrophils are the most striking feature. This may, in part at least, be due to the fact that the neutrophil of the normal monkey shows an average of 5 to 6 nuclear lobes in contrast to the normal average of 2 to 3 in the neutrophil of the human.

With careful recollection and review of the bizarre changes seen in marrow from humans megaloblastic anemia, preliminary attempts at evaluation of the changes in the marrow of monkeys with megaloblastic anemia have been made.

First, because the experimental production of megaloblasts has been such a debatable point, it was necessary that the process be allowed to proceed until completely typical megaloblasts were present. This was preceded by easily recognizable changes in the neutrophils in the majority of the monkeys, the changes in developing erythrocytes being less clearly classifiable.

Second, in order that as much information as possible be obtained from a single animal, various combinations of therapy (including vitamins B_{12}, C, and PGA)were employed. For example, since the clinical status of the monkeys continued its downward trend with injections of B_{12} alone, further evaluation of the changes seemed incompatible with the life of the animals.

The following interpretation has been given to the changes following therapy in monkeys which developed megaloblastic anemia.

The initial therapy in three monkeys was vitamin B_{12} alone. In monkey #14, which survived the anemia, no distinguishing change was seen in the marrow differential after 40 hours. In monkey #15, which also survived the anemia, there may have been a very slight shift to the right in cells of the megaloblastic series after 54 hours. In monkey #17, which died despite subsequent therapy, there appeared to have been no remarkable change in the marrow after 72 hours. The changes, if any, produced by administration of Vitamin B_{12}, then, seem less obvious than one would expect with an entirely effective therapeutic agent.

Two monkeys were given Vitamin C as the initial form of therapy. In monkey #8, the marrow had shown considerable reversion toward the normal pattern in 7 days although evidence of megaloblastic anemia remained. In 11 days there had been even more remarkable change. PGA was administered but the animal died 15 minutes later. In monkey #9, evidence of pathologic regeneration of erythrocytes was apparent. Increased mitoses in developing red cells were seen 2 days after the administration of Vitamin C, and relative percentages of developing erythrocytes remained elevated for five days following the initial administration of Vitamin C. There followed a period of increased erythropoiesis. In monkey #8, it would appear that although administration of Vitamin C seemed associated with an identifiable change in the marrow pattern, death was not prevented. In monkey #9, full-blown megaloblastic anemia seemed to have been avoided by

early administration of Vitamin C.

All of the monkeys which survived were eventually given Vitamin C. Except in those monkeys already described, Vitamin C was administered in combination with or following B_{12} or PGA. In monkey #17, however, there was some opportunity to evaluate the action of Vitamin C. After a 72-hours course of B_{12}, the marrow pattern remained that of a severe megaloblastic anemia. Vitamin C was administered, and 48 hours later there appeared to be some reversion toward the normal marrow pattern. The response was probably not adequate, however, because even though the monkey was then given PGA, he expired in 16 hours.

Vitamins B_{12} and C were administered simultaneously as the initial form of therapy in monkey #12. Although the degree of megaloblastic anemia present prior to therapy was not as pronounced as in some of the monkeys, the characteristic changes were not questionable. Twenty-four hours after B_{12} and C had been given, there was a remarkable change in the marrow pattern. In the subsequent 24 hours, there was a remarkable further reversion toward the normal pattern. Although one test of this type warrants no sweeping conclusions, the results here seemed dramatic. The impression derived is that the simultaneous administration of B_{12} and C is followed by a rapid response in the marrow.

Administration of PGA was routinely followed by a change in the marrow pattern. The dramatic changes were best followed in monkeys #14 and #15. Monkey #14 had been used for evaluation of B_{12} for 40 hours. Then, PGA was administered, and the marrow was examined at 6 and 21 hours. A shift to the right with maturation of megaloblasts was seen in the 6 hour specimen. Further evidence of this shift and of reversion to a normal marrow pattern was seen in the 21 hour specimen. Vitamin C was then administered, and the changes in the marrow continued the favorable trend which appeared to have been initiated by the administration of PGA. Monkey #15 had been used for the evaluation of B_{12} for 54 hours. PGA was then given, and the marrow was examined at 21 and 48 hours. Profound change, similar to that seen in monkey #14, was present in 21 hours. By 48 hours, only a few of the changes suggested the previously existing marked megaloblastosis of the marrow.

Monkey #12, given B_{12} and C, had shown dramatic changes in the marrow in 48 hours. PGA was then administered. There followed further reversion of the marrow toward a normal pattern, but it was not possible to evaluate the actual contribution of PGA to this change.

In monkey #13, the degree of original megaloblastosis of the marrow was not severe. PGA was given as the initial form of therapy. Undisputable evidence of megaloblastic anemia remained for 24 hours although there was a prompt change in the marrow pattern. After 8 days there was no evidence by which one could diagnose megaloblastic anemia although there was a persistent normoblastic hyperplasia.

PGA, then, seems to have caused a prompt reversion of the marrow pattern toward normal in the three instances in which it was possible to evaluate the change. Since this result had been anticipated early on the basis of the dramatic change in monkey #14, PGA was withheld in most of the experiments and attempts at discovering the action of vitamins B_{12} and C were made. Consequently only one animal, monkey #13, was given PGA as the original form of therapy. As indicated, the results of this therapy were satisfactory, but since the megaloblastic anemia was not in as severe a stage as that seen in monkeys #14, #15, and #17, caution should be exercised in comparing the results of PGA therapy in monkey #13 with the results of B_{12} therapy in the monkeys which were in severe relapse prior to therapy.

The overall results of this study are summarized in the accompanying tables. This study is preliminary, but the present clues to understanding of the parts played by the various therapeutic agents seem sufficiently clear-cut to warrant their

presentation. Some of the critical stages in the transformation of a megaloblastic to a normoblastic marrow have been obtained. Study of many serial biopsies of the marrow, probably best obtained during the first 48 hours, should provide much valuable information concerning the nature of normal and abnormal erythropoiesis.

Relation of Experimental Megaloblastic Anemia to Megaloblastic Anemia of Infants

A comparison of the syndromes exhibited by the infants and the monkeys with megaloblastic anemia reveals a close similarity in symptoms and course, namely; insidious onset of anorexia, increasing gradually as pallor appears, and the terminal stormy phase with profound anorexia and pallor, leucopenia, diarrhea, anemia and megaloblastic marrow.

One might well raise a question as to the frequency of deficiency of vitamin C in infants developing megaloblastic anemia. It has already been mentioned that scurvy was discovered in approximately 25% of reported cases of megaloblastic anemia in infancy, and fully 50% of the reported cases had a history of grossly inadequate intake of vitamin C. The status of the infants as regards saturation with vitamin C was not given in any of the papers quoted. Suggestive circumstantial evidence may be provided by noting the fact that the age distribution of megaloblastic anemia in infants coincides with that of scurvy, both being most common between 5 and 9 months of age and rare after one year. Compare fig. 1[6] and fig. 3[5]. The patients thus far reported were collected largely in 1944 and 1945 when the incidence of scurvy was at a peak (see[15], fig. 1) as it tends to be in disturbed times like war and post-war periods. Very few cases of scurvy or megaloblastic anemia are being see at present.

A more convincing item of circumstantial evidence is the complete disappearance of megaloblastic anemia within the past two years amongst the infants being fed the proprietary infant foods suspected in the reports of Zuelzer and Aldrich and Nelson and tested in this investigation. Until two years ago these foods did not contain any vitamin C. The physician was expected to prescribe this vitamin along with the food as is still the case with evaporated and pasteurized cow milk formulae. Unfortunately, all too frequently infants do not receive such supplementary vitamins through either misunderstanding and neglect on the part of the physicians and parents or refusal by the infants. During the past two years, vitamin C has been included in the proprietary foods under consideration in such amounts as to insure an adequate intake of vitamin C without supplementation. There have been no cases of megaloblastic anemia reported occurring in infants fed these two proprietary infant foods since vitamin C has been included.

Infants with megaloblastic anemia reported recently[16] have been fed with formulae which still depend upon supplementation with vitamin C such as evaporated cow milk and evaporated goat milk. Amatos' report of 25 infants developing megaloblastic anemia after prolonged feeding at the breast might be explained as due to deficiency of vitamin C or other substances in the breast milk because of poor diets probably available for the mothers in Naples during the war when his series was collected. Our experiment with human milk demonstrated that megaloblastic anemia developed if a monkey was fed human milk obtained from mothers on adequate diets but boiled to destroy its vitamin C content. We have found that the PGA content of fresh human milk is no greater than that in the other milks used in these experiments. (Table II)

Two instances of megaloblastic anemia were reported in "celiac disease" which the authors admit is quite exceptional and the vitamin C status of the reported cases was not stated.[17]

It would seem reasonable to insist

that the details of the vitamin C status of individuals developing megaloblastic anemia will have to be made clear in each case before the mechanism described in this report can be excluded. We have already emphasized that there are several ways in which a deficiency of hematopoietic factors might arise. (Table I) A deficiency of PGA conditioned by chronic deficiency of ascorbic acid is but one way, albeit an important one, apparently.

A schematic comparison of the features of megaloblastic anemia in infants with that in the experimental monkey as given in Table V may serve as a fitting conclusion. Further discussion of the significance of these experiments would lengthen the report unduly and is not required for the purpose of relating the experimental anemia to the naturally occurring disease in infants. It may be pointed out that herein is contained further evidence that vitamin B_{12} cannot convert a megaloblastic anemia to

Table V

MEGALOBLASTIC ANEMIA

Features	Infants	Exp. Animals
Clinical features	Same	Same
Vitamin B_{12}	Effect irregular	No effect
PGA	Prompt response	Prompt response
Vitamin C	May respond	Responds
"Spontaneous" cure s C	Not reported	Never
Milk diets + C	M. Anemia rare	No anemia
Milk diets s C	M. Anemia frequent	M. Anemia regularly
3.3% Milk protein s C	Not prevented	Not prevented
PGA prevents s C	?	Yes
M. Anemia & C deficiency	Frequently associated	Regular association
Past history of:		
Malabsorption	Infrequently associated	Not present and unnecessary
Starvation		
Infections		
Maternal Malnutrition		

normal when PGA is deficient.[18,19,20] Ascorbic acid deficiency alone does not cause megaloblastic anemia. (See monkey #14B, Table III) Presumably vitamin C therapy permits cure of the megaloblastic anemia only because it makes PGA available by a reversal of the mechanism by which the deficiency of vitamin C led to PGA deficiency. Finally, it should be noted that vitamin B_{12} may also be deficient in these experimental animals as well as the patients. Definitive data concerning tissue stores of vitamin B_{12} are not available in either case. The difficulty in reasoning from response to administration of vitamin B_{12} [16] should be apparent when one considers that vitamin C given previously or at the same time may make PGA available, and that without PGA, B_{12} is apparently ineffective.

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II. MEDICAL SCHOOL NEWS

Coming Events

January 30- February 11 - Continuation course in Neurology for Internists, Psychiatrists, and Pediatricians.

January 31 - J. B. Johnston Lecture - "Cortical Localization" - Theodore Rasmussen of the University of Chicago, 8:00 p.m., Natural History Museum Auditorium.

February 9 - Dean Harold S. Diehl; "A Report on British Medical Education Under the National Health Act"; 3:00 p.m., Medical Science Amphitheater; sponsored by the Minnesota Medical Foundation.

February 16 - E. Starr Judd Lecture - "Growth in the Field of Anesthesia" - Henry K. Beecher, Harvard University Medical School; Museum of Natural Science Auditorium, 8:15 p.m.

February 16-18 - Continuation course in Cancer for General Physicians.

March 6-8 - Continuation course in Gastro-Intestinal Diseases for General Physicians.

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Continuation Course in Neurology

Four distinguished visiting faculty members will participate in the continuation course in Clinical Neurology to be presented at the Center for Continuation Study, January 30 to February 11. Dr. Theodore Rasmussen, Professor of Surgery and Chief of Neurological Surgery at the University of Chicago, will participate in the course and will deliver the annual J. B. Johnston lecture at 8:00 p.m. in the auditorium of the Museum of Natural History. Dr. Rasmussen's subject will be, "Cortical Localization". Everyone interested is invited to attend this lecture.

Other visiting faculty members are Dr. Walter Klingman, Professor of Neurology, University of Virginia Hospital, Charlottesville, Virginia; Dr. Harold C. Voris of the Division of Neurological Surgery, Mercy Hospital, Chicago; and Dr. A. Earl Walker, Professor of Neurological Surgery, Johns Hopkins University. The remainder of the faculty of the course will be made up of members of the staff of the University of Minnesota Medical School and the Mayo Foundation.

* * *

Dean Diehl to Give Lecture on British Medical Education

Dean Harold S. Diehl will deliver a special address before students and faculty of the medical school February 9 at 3:00 p.m. in the Medical Science Amphitheater. The lecture sponsored by the Minnesota Medical Foundation will give the medical school an opportunity to hear first hand Dean Diehl's report on British medical education under the National Health Act.

Dr. Diehl is at present in the British Isles conducting a survey at the request of the American Medical Association. His lecture here will be his first report on this subject in Minnesota.

* * *

New Minnesota Medical Foundation Members and Patron Members

Ivan Baronofsky, M.D., St. Paul
F. J. Schatz, M.D., St. Cloud
Arnold J. Kremen, M.D., Minneapolis
S. A. Weisman, M.D., Los Angeles, Cal.
A. R. Varco, M.D., St. Louis Park
John C. Benson, Minneapolis
Mrs. Ida B. Williams, Minneapolis
Mrs. Grace B. Dayton, Minneapolis
Charles A. Ward, St. Paul
I. A. O'Shaughnessy, St. Paul

III. UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
CALENDAR OF EVENTS

January 29 - February 4, 1950

No. 275

Sunday, January 29

9:00 - 10:00 Surgery Grand Rounds; Station 22, U. H.

10:30 - 11:00 Surgical Conference; Continuous Stellate Ganglion Block in Apoplexy; Ellis N. Cohen; Rm. M-109, U. H.

Monday, January 30

8:00 - Fracture Rounds; A. A. Zierold and Staff; Ward A, Minneapolis General Hospital.

9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; M-109, U. H.

10:00 - 12:00 Neurology Rounds; A. B. Baker and Staff; Station 50, U. H.

11:00 - Pediatric Rounds; Erling Platou; Sta. I, General Hospital.

11:00 - 11:50 Physical Medicine Seminar; E-101, U. H.

11:00 - 11:50 Roentgenology-Medicine Conference; Veterans Hospital.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Eustis Amphitheater, U. H.

12:00 - 1:00 Physiology Seminar; Pulmonary Hypertension; Richard Ebert; 214 M. H.

12:15 - 1:20 Obstetrics and Gynecology Journal Club; Staff Dining Room, U. H.

12:30 - 1:20 Pathology Seminar; The Production of Bacterial Endocarditis in Dogs with Arteriovenous Fistula; C. W. Lillehei; 104 I. A.

12:30 - 1:30 Surgery Problem Case Conference; A. A. Zierold, C. Dennis and Staff; Small Classroom, Minneapolis General Hospital.

1:30 - 2:30 Surgery Grand Rounds; A. A. Zierold, C. Dennis and Staff; Minneapolis General Hospital.

1:30 - 2:30 Pediatric-Neurological Rounds; R. Jensen, A. B. Baker and Staff; U.H.

4:00 - Public Health Seminar; Subject to be announced; 113 Medical Sciences.

4:00 - Pediatric Seminar; Immunization; Dr. Child; 6th Floor West, Child Psychiatry, University Hospitals.

5:00 - 5:50 Clinical Medical Pathologic Conference; Todd Amphitheater, U. H.

5:00 - 6:00 Urology-Roentgenology Conference; D. Creevy, O. J. Baggenstoss and Staffs; M-109, U. H.

Tuesday, January 31

8:15 - 9:00 Roentgenology-Surgical-Pathological Conference; Craig Freeman and L. G. Rigler; M-109, U. H.

8:30 - 10:20 Surgery Conference; Small Conference Room, Bldg. I, Veterans Hospital.

9:00 - 9:50 Roentgenology Pediatric Conference; L. G. Rigler, I. McQuarrie and Staffs; Todd Amphitheater, U. H.

10:30 - 11:50 Surgical Pathological Conference; Lyle Hay and E. T. Bell; Veterans Hospital.

11:00 - Contagion Rounds; Forrest Adams; Sta. L, General Hospital.

12:30 - Pediatric-Surgery Rounds; Drs. Stoesser, Wyatt, Chisholm, McNelson and Dennis; Sta. I, Minneapolis General Hospital.

12:30 - 1:20 Pathology Conference; Autopsies; J. R. Dawson and Staff; 102 I. A.

1:30 - 2:30 Pediatric Psychiatry Conference; R. A. Jensen and Staff; 6th Floor, West Wing, U. H.

1:00 - 2:30 X-ray Surgery Conference; Auditorium, Ancker Hospital.

2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III, Veterans Hospital.

3:15 - 4:20 Gynecology Chart Conference; J. L. McKelvey and Staff; Station 54, U. H.

3:30 - 4:20 Clinical Pathological Conference; Staff; Veterans Hospital.

4:00 - 5:00 Physiology-Surgery Conference; Experimental Coarctation; Wm. Clatworthy; Eustis Amphitheater.

4:00 - 5:00 Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.

5:00 - 6:00 Porphyrin Seminar; C. J. Watson, Samuel Schwartz, et al; Powell Hall Amphitheater.

Wednesday, February 1

8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M-109, U. H.

8:30 - 9:30 Clinico-Pathological Conference; Auditorium, Ancker Hospital.

8:30 - 10:00 Orthopedic-Roentgenologic Conference; Edward T. Evans; Room 1AW, Veterans Hospital.

8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker; Veterans Hospital.

11:00 - Pediatric Rounds; Erling Platou; Sta. I, General Hospital.

11:00 - 12:00 Pathology-Medicine-Surgery Conference; Medicine Case; O. H. Wangensteen, C. J. Watson and Staffs; Todd Amphitheater, U. H.

Wednesday, February 1 (Cont.)

12:00 - 1:00 Radio-Isotope Seminar; The Use of Cu^{64}, Mo^{99}, and P^{32} in the Study of Mineral Metabolism in Animals; Leon Singer; 113 Medical Sciences.

12:15 - Staff Meeting; Main Classroom, General Hospital.

3:00 - Pediatric Rounds; E. J. Huenekens; Sta. I, General Hospital.

3:30 - 4:30 Journal Club; Surgery Office, Ancker Hospital.

4:00 - 5:00 Infectious Disease Rounds; Veterans Hospital, Main Conference Room, Bldg. I.

5:00 - 5:50 Urology-Pathological Conference; C. D. Creevy and Staff; E-101, U. H.

Thursday, February 2

8:30 - 10:20 Surgery Grand Rounds; Lyle Hay and Staff; Veterans Hospital.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; M-109, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:50 Surgery-Radiology Conference; Daniel Fink and Lyle Hay; Veterans Hospital.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Todd Amphitheater, U. H.

11:30 - Pathology Conference Clinic; Main Classroom; General Hospital.

11:30 - 12:30 Clinical Pathology Conference; Steven Barron, C. Dennis, George Fahr, A. V. Stoesser and Staffs; Large Classroom, Minneapolis General Hospital.

12:00 - 1:00 Physiological Chemistry Seminar; Synthesis and Biological Effects of Vitamin A Compounds; Paul Richardson; 214 M. H.

1:00 - 1:50 Fracture Conference; A. A. Zierold and Staff; Minneapolis General Hospital.

2:00 - 3:00 Errors Conference; A. A. Zierold, C. Dennis and Staff; Large Classroom, Minneapolis General Hospital.

4:15 - 5:00 Bacteriology and Immunology Seminar; The Anti-bacterial Action of the Degradation Products of Chlorophyl; William D. McBride; 214 M. H.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.

5:00 - 6:00 X-ray Seminar; Presentation of Miller Hospital Cases; Drs. Peterson and Paulson; Todd Amphitheater, U. H.

7:30 - 9:30 Pediatrics Cardiology Conference and Journal Club; Review of Current Literature 1st hour and Review of Patients 2nd hour; 206 Temporary West Hospital.

Friday, February 3

8:30 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:20 Medicine Grand Rounds; Veterans Hospital.

10:30 - 11:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.

11:00 - Pediatric Rounds; Erling Platou; Sta. I, General Hospital.

11:00 - 12:00 Surgery-Pediatric Conference; C. Dennis, O. S. Wyatt, A. V. Stoesser, and Staffs; Minneapolis General Hospital.

11:45 - 12:50 University of Minnesota Hospitals General Staff Meeting; Hemolysis During Trans-urethral Resection; Its Influence on Operative Mortality: Robert N. Evert; Powell Hall Amphitheater.

12:00 - 1:00 Surgery Clinical Pathological Conference; Clarence Dennis and Staff; Large Classroom, Minneapolis General Hospital.

1:00 - 1:50 Dermatology and Syphilology Conference; Presentation of Selected Cases of the Week; H. E. Michelson and Staff; W-312, U. H.

1:00 - 3:00 Pathology-Surgery Conference; Auditorium, Ancker Hospital.

1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.

3:00 - 4:00 Neuropathology Conference; F. Tichy; Todd Amphitheater, U. H.

3:00 - 6:00 Demonstrations in Cardiovascular Physiology; M. B. Visscher, et al; 301 M. H.

4:00 - 5:00 Clinical Pathological Conference; A. B. Baker; Todd Amphitheater, U. H.

4:15 - 5:15 Electrocardiographic Conference; Demonstration; G. N. Aagaard; 106 Temp. Bldg., Hospital Court, U. H.

5:00 - 6:00 Otolaryngology Seminar; Review of Current Literature; Dr. Kusske; Discussor, Dr. Priest; Todd Memorial Room, U. H.

Saturday, February 4

7:45 - 8:50 Orthopedics Conference; Wallace H. Cole and Staff; M-109, U. H.

8:00 - 9:00 Surgery Literature Conference; Clarence Dennis and Staff; Small Classroom, Minneapolis General Hospital.

8:30 - 9:30 Surgery Conference; Auditorium, Ancker Hospital.

Saturday, February 4 (Cont.)

9:00 - 11:30 Psychiatry Conference; Group Therapy; Drs. Simon and Hales; Powell Hall Amphitheater, U. H.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; E-221, U. H.

9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater, U. H.

9:00 - 11:30 Surgery-Roentgenology Conference; Todd Amphitheater, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

11:00 - 12:00 Anatomy Seminar; Retrograde Degeneration of Nerve Cells; Berry Campbell; Steroid Hormones and Carbohydrate Metabolism; Lewis O. Ingersoll; 226 I. A.

11:00 - Contagion Rounds; Forrest Adams; Sta. L, General Hospital.