no 2

Bulletin of

Staff Meeting

Minnesota General Hospital
University of Minnesota

Aplastic Anemia

VOL. V THURSDAY, OCTOBER 12, 1933 NO. 2

INDEX

I. MEETINGS:

1. STAFF MEETING:

Date: October 5, 1933.

Place: Recreation Room, Nurses' Home.

Time: 12:15 to 1:15.

Attendance: 121

Program: Purpose of Staff Meetings
Spontaneous Hypoglycemia

Discussion: Alex Blumstein
H. A. Reimann
W. L. Boyd
C. P. Fitch
S. Marx White
Cyrus O. Hansen
Irvine McQuarrie
Bernard A. Watson
Fred Jarvis
U. S. Anderson

Theme: The first case, pgs. 3-4, was seen in 1931. Although a diagnosis of functional neurosis was made, it was by no means a satisfactory explanation of the patient's complaints. We learned that he later consulted the Mayo Clinic and we identified him in Dr. Judd's report by the history. At one time, it was not thought that malignant growths were able to function. This has been discredited by the recent work on tumors of the ductless glands (basophile-adenoma of pituitary gland, ovarian tumors, pancreatic, etc.). Tumors of the adrenal should also be included. Hypoglycemia has been extensively investigated in cattle. Most of the cases proved to be hypocalcemia (milk fever). Experimental production of hypoglycemia by injection of insulin in cattle is difficult. One case which was apparently successful was later found to be due to deficient calcium. A condition not unlike pre-eclamptic toxemia is observed in sheep, especially with multiple pregnancies. Blood sugar determinations on hypotensive subjects with early morning weakness did not reveal significant changes. Although some "epileptics" with early morning seizures were later found to be instances of hypoglycemia, blood sugar determinations of more than 200 epileptics made by one of us did not show any variation. A university student who obtains relief from weakness by eating candy bars was studied. He showed a variation in his blood sugar after exercise. Routine blood sugars on normal university students showed marked variation. Care should be exercised in making a diagnosis of clinical hypoglycemia on blood sugar findings alone. The picture is probably variable and the patient should be seen during the attack. Alternating hypo and hyperglycemia was described. The patient needed insulin part of the day and sugar the rest. The hypoglycemic attacks so closely simulated insulin shock that the home physician in Iowa made such a diagnosis although the patient had not had insulin for 6 months. He referred him back for study because of the peculiar attacks and he is now being investigated in the University of Iowa Hospital. A patient who was thought to have a tumor of the pancreas was explored recently at the Mayo Clinic and was found to have extensive liver damage and no tumor of the pancreas. Liver functional tests had been negative. Hypoglycemic attacks can occur in a variety of conditions. The pituitary, adrenal and liver may be responsible and not all are due to tumors of the pancreas. It is interesting to note that tumors of the liver are known to cause the disorder. The failure to recognize the condition is most often due to not keeping it in mind. Narcolepsy may be associated disorder. We have followed several such cases and deep sleep is induced by various causes (laughter, food, etc.). Ephredin seems to have a beneficial influence. Several interesting examples of the condition were described.

Gertrude Gunn,
Record Librarian

2. MEDICAL ALUMNI ASSOCIATION

The sixth annual clinical meeting of the Minnesota Medical Alumni Association will be held Friday,

October 27, 1933, at the University Hospital in Minneapolis. This meeting will be the day before Minnesota's Homecoming game with Iowa. There will be a luncheon at the University Hospital for those attending the meeting. All persons interested in attending the meeting will be welcome.

The following program will be presented:

Morning Session
9:00 A.M.

E. L. Gardner, M.D.,
Chairman.

Skin Clinic
John Madden, M.D., St. Paul

Injection Treatment of Hernias
A. F. Bratrud, M.D., Minneapolis

The Role of Calcium in Medical Treatment
Reuben Johnson, M.D., Minneapolis

Childhood Tuberculosis
C. A. Stewart, M.D., Minneapolis

Subject to be announced
Lawrence R. Gowan, M.D., Duluth

Obstetric Comments
Fred Adair, M.D., Chicago, Ill.

Luncheon and Business Meeting,
University Hospital
Richard E. Scammon, Ph.D., Minneapolis.
Edward D. Anderson, M.D.,
Minneapolis.

Afternoon Session
2:00 P.M.

O. S. Wyatt, M.D.,
Chairman.

The Role of Arsenic in Causing Polyneuritis
W. D. Shelden, M.D., Rochester

Pyuria
W. Downing, M.D., LeMars, Iowa.

Symptoms of Refractive Error
Merritt W. Wheeler, M.D., St. Paul

Surgery--Subject to be announced
W. O. Ramstad, M.D., Bismarck, N.D.

Shoulder Joint Injuries
Joseph R. Kuth, M.D., Duluth

The X-ray in Treatment
Russell Gates, M.D., Minot, N. D.

Once a year, the Medical Alumni Association of the University of Minnesota return to their Alma Mater and go back to school for one day. The teachers are all members of the Alumni Association. This custom, started a few years ago, has proven very popular. You are welcome at any of the meetings no matter what your school.

3. THE ASSOCIATION OF AMERICAN MEDICAL COLLEGES

will hold its Forty-Fourth Annual Meeting in Rochester, October 30; Minneapolis, October 31 and November 1, 1933, under the presidence of Louis B. Wilson. The program will be as follows:

Monday, October 30
At Rochester--9:30 A.M.

Symposium on the Report of the Commission on Medical Education
Relation of the Number of Medical Graduates to the Public Need.
W. C. Rappleys, Dean Columbia University College of Physicians and Surgeons.
William D. Cutter, Secretary Council on Medical Education and Hospitals, American Medical Association.
C. R. Bardeen, Dean University of Wisconsin Medical School (Representing the State University).
C. C. Bass, Dean Tulane University of Louisiana School of Medicine (Representing the Endowed University).
General Discussion.

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6:30 P.M. Dinner (informal).
L. D. Coffman, President University of Minnesota, will deliver an address at the dinner.

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Tuesday, October 31
At Minneapolis---9:30 A.M.

Symposium: Medical Care of the American People; Income and Distribution of Physicians

A. M. Schwitalla, Dean St. Louis University School of Medicine (Member of Committee on Cost of Medical Care).
R. C. Buercki, Superintendent Wisconsin General Hospital.
Ray Lyman Wilbur, President Stanford University (Chairman Committee on the Cost of Medical Care).

General Discussion.

Report of Committee on Aptitude Test
F. A. Moss, Secretary of the Committee.
Discussion to be opened by J. M. H. Rowland, Dean University of Maryland School of Medicine.

Discussion.

Administration of Clinical Clerkships
Rufus Q. Goodwin, University of Oklahoma School of Medicine.

Discussion.

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2:30 P.M. Demonstration of Student Health Activities in the University of Minnesota.

H. S. Diehl, Director.

6:30 P.M. Dinner (Hotel Nicollet)

8:00 P.M. Executive Session (Hotel Nicollet)

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Wednesday, November 1
At Minneapolis---9:30 A.M.

The Relation of Certain Factors in the Student's Premedical Record to Success in Medical School.
George R. Moon, University of Illinois College of Medicine.

Social Case Teaching of Medical Students.
Ida M. Cannon, Chief of the Social Service Department of the Massachusetts General Hospital.

Discussion.

Bedside Teaching of Medicine.
1. Reginald Fitz, Harvard University Medical School.
2. Maurice Pincoffs, University of Maryland School of Medicine.

Discussion.

Study of Accomplishment of Students in High School, College and Medical School.
F. S. Randles, Albany Medical College.

Discussion.

Problems of the Lowest Third of the Student Body.
R. M. Strong, Loyola University School of Medicine.

Discussion.

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As you will note, the formal program consists of half-day sessions. The remainder of each day is spent visiting the local school. The Arrangement Committee would appreciate it if you would be available during the Minneapolis days. Practically every Medical School is a member and the majority will send delegates. This is an unusual opportunity to show the other Medical Schools what we are trying to do. You are welcome to attend their meetings which will probably be held in the Hospital. It is up to us to show them what a real host Minnesota can be.

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---His host of friends wish him all the

success in the world--.

III. CASE REPORT

APLASTIC ANEMIA

Path. Rudolph Koucky.

Case is that of a 21-year old male observed in the Health Service Out-Patient Department from 1926 to 1933 in various examinations through high school and college. Admitted to Health Service Hospital 4-22-33 and discharged 6-15-33. Taken care of by a private physician from this time until death on 8-10-33.

6 Yrs. of Health Examination: Colds, Dental Caries.

9-24-26 (age 14) - Routine health examinations done in University High School. No past illnesses listed. Physical examination entirely negative except for dental caries.

9-21-27 - Periodic health examination. Complaint of pleurisy now listed. Physical examination negative except for dental caries.

9-26-28 - Periodic health examination. Family history: Paternal grandfather had apoplexy and kidney trouble. Maternal grandmother had sick headaches. Past illnesses: Measles at 9, pleurisy at 14. Complaints: Earache, ringing in ears, occasional nosebleed, belching. Weight - 130 lbs., usual weight - 135. Physical examination: Dental caries. Palpable thyroid.

2-17-30 - H.S.Out-Patient Department. Patient has been in the dispensary on a few occasions through his high school years with sore throat, nasopharyngitis and once with influenza. Came in today complaining of a cold.

4-17-30 - H.S. O.P.D. - Another cold.

5-19-30 - H.S. O.P.D. - Acute respiratory infection.

7-31-31 - H.S. O.P.D. - Laceration from a saw which healed without infection.

2-15-32 - H.S. O.P.D. Acute pharyngitis.

4- 7-33 - H.S. O.P.D. - Pain in left foot on walking, present for 4 or 5 weeks. Appears to be a slight icteric tinge to the sclerae. No symptoms. Urine negative for bile.

4-12-33 - H.S. O.P.D. Diagnosis of metatarsalgia made. Brace fitted.

Headache, Anemia

4-21-33 - H.S. O.P.D. Headache in posterior part of head (about 2 weeks), more or less constant, increased on exercise. Feels tired. Appetite normal. Constipation slight. Frequent urination. Past 2 weeks noted petechial hemorrhages in skin. Examination: Pale. Lungs negative. Heart - murmur at apex. Abdomen - negative. Rbc's 2,850,000, Blood - wbc's 1,400, Hb. 53%, Pmn 44%, L 52%, E 2%, M 2%.

Aplastic Anemia. Nucleotide begun.

4-22-33 - Admitted. Blood work checked twice - wbc's 800 and 900, rbc's 2,500,000, Hb. 55%, 60% L. Platelet count - 40,000. These findings and presence of petechiae makes the picture appear like aplastic anemia or agranulocytosis without apparent angina. Blood transfusion of 500 cc. citrated blood. Nucleotide .5 gram intramuscularly. Following this, chill occurred and temperature rose to 103.6.

Reaction

4-23-33 - Blood - 11 A.M. - wbc's 1,700, 6 P.M. - wbc's 1,200, pmn's 52%, L 48%. Hb. 60%, rbc's 3,160,000. .5 and .7 gram nucleotide given in 2 injections. Both of these followed in 2 hours by a severe chill and reaction consisting of temperature of 102 and 104, respectively. Very uncomfortable.

X-ray

4-24-33 - Blood - 9 A.M. - wbc's 1,300, 8 P.M. - 1,100. Differential - 58% Pmn's, 42% L, Hb. 62%, rbc's 3,050,000. Uncomfortable following injection of nucleotide. Has considerable pain at site of injection. X-ray of chest, sinuses - No gross evidence of disease in lungs. Distinct cloudiness of right maxillary sinus near base, suggesting some granulation or possibly polyp. Remaining sinuses clear.

4-day Course of Nucleotide

4-25-33 - Nucleotide given in morning and evening. Very tired. Some pain in the back. Complains of aching eyes. Seems slightly confused. Temperature rises to 102.8. Stool - benzidene negative. Blood - wbc's 850, Hb. 60%.

Epistaxis

4-26-33 - 400 cc. blood given. Slight oozing from right nostril. Adrenalin pack applied. Oozing continues through most of day. Blood picture - 800 wbc's, rbc's 2,240,000, Hb. 52%. Bone concentrate (Watkin's) by mouth started, 100 capsules given.

4-27-33 - Wbc's 700, rbc's 2,800,000, Hb. 50%, Pmn's 27% (very toxic), L 71%, M 2%. Nucleotide has been discontinued because of severe reaction patient has been having. Feels very uncomfortable. Temperature 103.6. Calcium gluconate gr. xv, 4 times a day. 15 capsules bone marrow, 3 cc. liver extract also given. Bone marrow given by mouth and liver extract intramuscularly. Temperature normal.

4-28-33 - Condition is stationary except that granulocytes are still falling. Temperature 100.8.

4-29-33 - 450 cc. citrated blood.

Epistaxis - No response to treatment

4-30-33 - Wbc's 900, Hb. 56%. Bone marrow continued by mouth and liver extract intramuscularly. Calcium gluconate continued. Complains of being tired. Has headache. Severe epistaxis, stopped by pack.

5-1-33 - Wbc's 700, rbc's 2,700,000, Hb. 51%. Treatment as before. Epistaxis again.

No regeneration

5-2-33 - Wbc's 850, rbc's 2,700,000, Hb. 52%, reticulocytes .2%. Temperature slightly elevated daily, ranging up to 99.4.

5-3-33 - Still having bleeding from nose (moderate amount). Calcium gluconate, bone marrow and sedatives for the frequent headaches continued.

5-5-33 - Wbc's 1,200, rbc's 2,620,000, Hb. 48%. Complains of headache and has oozing from nose from time to time.

5-7-33 - Wbc's 925, rbc's 2,710,000, Hb. 48%, Pmn's 26%, L 74%, reticulocytes .2%.

More Transfusions

5-8-33 - Transfusion 400 cc. Temperature fluctuates from normal to 99.8.

5-9-33 - Wbc's 1,125, rbc's 2,800,000, Hb. 50%. Temperature 100.6.

5-11-33 - Wbc's 700, rbc's 2,800,000. Feels somewhat better although is somewhat weak.

5-13-33 - wbc's 1,600, rbc's 2,670,000, Hb. 45%. Treatment now consists of calcium gluconate and haliver oil and ultra violet light. Bone marrow has been discontinued.

5-17-33 - Wbc's 1,100, rbc's 2,720,000, Hb. 42%.

5-18-33 - 725 cc. citrated blood given. Feeling considerably better.

Improvement

5-20-33 - Wbc's 1,200, rbc's 3,080,000, Hb. 60%.

5-23-33 - Wbc's 1,500, rbc's 2,980,000, Hb. 58%. Treatment with calcium gluconate and haliver oil continued. Jeculin oz. $\frac{1}{2}$, three times a day added.

5-25-33 - Wbc's 2,000, rbc's 3,130,000, Hb. 58%. Temperature normal.

5-27-33 - Wbc's 2,000, rbc's 3,000,000, Hb. 53%.

5-30-33 - Wbc's 2,600, rbc's 2,800,000, Hb. 50%. Comfortable; no fever.

5-31-33 - Wbc's 2,600, rbc's 2,700,000. Numerous petechiae over entire body. Uncomfortable.

6-1-33 - Wbc's 1,200, rbc's 3,030,000, Hb. 48%. Complains of being tired and has a headache.

6-2-33 - 750 cc. citrated blood given.

6-3-33 - Wbc's 1,800, rbc's 3,255,000, Hb. 55%.

6-6-33 - Wbc's 1,700, Hb. 58%, rbc's 3,320,000. Fairly comfortable, tired. Treatment as before. Temperature approximately normal, few rises to 99.

6-8-33 - wbc's 1,600, Hb. 57%,

rbc's 2,810,000. Condition same.

6-10-33 - Wbc's 1,800, rbc's 3,150,000, Hb. 59%. No change.

6-13-33 - rbc's 1,900, rbc's 2,780,000, Hb. 54%.

6-14-33 - 800 cc. citrated blood. Complaining of pain in the calves of legs and throughout the feet. Also headache.

6-15-33 - Discharged for care by private physician at home.

Progressive course. Agranulocytosis. Stomatitis.

8-10-33 - Summary of course since leaving the hospital is approximately as follows: Course has been almost identical with that observed during hospital admission. Had a few complaints, weakness, headaches and oozing from the nose. Treatment was continued very much the same as previously. In addition, a course of adrenalin was tried but proved to be of no benefit. Had to be transfused approximately every 10 to 14 days. Hb. fluctuated from 50 to 35%. Granulocytes in the smear became progressively fewer in number and at times were very difficult to find. About July 15, developed stomatitis, ulceration of tongue and cheek. There was some fever and considerable bleeding from the mouth and nose. During this time, the granulocytes reached their lowest end and could hardly be found. August 1, definite improvement in the stomatitis and ulceration took place. Numerous petechiae have been present throughout. In the last two weeks of life, condition was unchanged, but he became progressively weaker. Bleeding from nose and mouth became more marked. Petechiae continued. A mass appeared in the left deltoid area. This was not apparently inflamed. Just prior to death, a nodule appeared in the muscles of the forearm under the elbow. No lymph nodes palpable at this time. Terminally, patient coughed up a great deal of bloody sputum. 1:30 P.M. - Expired.

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SUMMARY

Date	Hgb.	Rbc.	Reticulocytes	Wbc.	Pmn	L	Platelet	Treatment	Course
4-21-33	53	2.85	-	1400	44	52	-	See above	See above
4-22-33	55	2.50	-	800, 900	-	-	40,000	Transfusion (500 cc) - Nucleotide	" "
4-23-33	60	3.16	-	1700,1200	52	48	-	Nucleotide	" "
4-24-33	62	3.05	-	1300,1100	58	42	-	Nucleotide	" "
4-25-33	60	-	-	850	-	-	-	Nucleotide	" "
4-26-33	52	2.24	-	800	-	-	-	Transfusion (400 cc) - Bone Concentrate	" " " "
4-27-33	50	2.80	-	700	27	71	-	Calcium-Bone Marrow - Liver extract	
4-29-33	-	-	-	-	-	-	-	Transfusion (450 cc).	
4-30-33	56	-	-	900	-	-	-	Bone Marrow-Calsium - Liver Extract	Epistaxis.
5- 1-33	51	2.70	-	700	-	-	-	" "	" "
5- 2-33	52	2.70	0.2%	850	-	-	-	" "	Temp. 99.4
5- 5-33	48	2.62	-	1200	-	-	-	" "	Epistaxis-Headache.
5- 7-33	48	2.71	0.2%	925	-	-	-	" "	

Date	Hgb.	Rbc.	Reticulocytes	Wbc.	Pmn	L	Platelet	Treatment	Course
5- 8-33	-	-	-	-	-	-	-	Transfusion (400cc)	Temp. 99.8c
5- 9-33	50	2.80	-	1125	-	-	-	-	Temp. 100.6°
5-11-33	-	2.80	-	700	-	-	-	-	Better but weak.
5-13-33	45	2.67	-	1600	-	-	-	Calcium-Haliver Oil-Ultra-Violet Light	-
5-17-33	42	2.72	-	1100	-	-	-	-	-
5-18-33	-	-	-	-	-	-	-	Transfusion (725cc)	Feels better.
5-20-33	60	3.08	-	1200	-	-	-	-	Improved.
5-23-33	58	2.98	-	1500	-	-	-	Jeculin oz. ½ tid	-
5-25-33	58	3.13	-	2000	-	-	-	-	
5-27-33	53	3.00	-	2000	-	-	-		
5-30-33	50	2.80	-	2000	-	-	-		Comfortable - No fever.
5-31-33	-	2.70	-	2600	-	-	-		Petechiae - Uncomfortable.
6- 1-33	45	3.03	-	1200	-	-	-		Tired - Headache.
6- 2-33	-	-	-	-	-	-	-	Transfusion (775cc).	-
6- 3-33	55	3.25	-	1800	-	-	-		
6- 6-33	58	3.32	-	1700	-	-	-		
6- 8-33	57	2.81	-	1600	-	-	-		
6-10-33	59	3.15	-	1800	-	-	-		
6-13-33	54	2.78	-	1900	-	-	-		
6-14-33	-	-	-	-	-	-	-	Transfusion (825 cc)	Pain in legs.
6-15-33	-	-	-	-	-	-	-		Headache.- Tiredness - Pains from time to time. Discharged.

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AUTOPSY

Anemia Petechiae

Body is that of a white male, about 21 years of age, measuring 176 cm. in length and weighing between 150 and 170 lbs. Skin is quite pale. The color in the lips has practically disappeared. Numerous petechiae are present over chest, thighs, back and arms. No subcutaneous lymph nodes palpable. There is a mass in the substance of the right deltoid. Round, hard, non-moveable mass in right upper forearm, apparently imbedded in the muscle. The pupils are equal and measure 4 mm. in diameter (each). The mouth is closed preparatory to embalming. It cannot be inspected. It is said that there are no ulcerations at this time. Body is very muscular. Nourishment fair. Rigor fully developed. Hypostasis purplish and posterior. No edema, cyanosis or jaundice. Subcutaneous fat rather scanty in amount

and has a yellowish color.

The Peritoneal Cavity is smooth and glistening, contains no excess fluid. No adhesions. The Appendix hangs free and is not inflamed. The diaphragm on the right is at the 4th rib; left at the 4th interspace. The diaphragm on the left side contains numerour petechial hemorrhages, some of which are confluent.

The Pleural Cavities contain no excess fluid. The Pericardial Sac appears normal. No excess fluid or adhesions.

Petechiae

The Heart weighs about 300 grams. It is quite firm. The musculature shows no infarctions or softening. The mural endocardium is smooth. The valves are well formed and show no recent or old vegetations. The vessels at the base have a normal relationship to each other. There are numerous petechiae present particularly on the anterior surface of the heart in the epicardium and a few in the endocardium of the left ventricle.

Bleeding. Atypical Pneumonia

The Right Lung weighs 850 grams, Left 500 grams. Both are completely expanded and collapse slowly. There is a little tenacious blood-tinged mucus in the bronchi. The bronchi are pale and mucosa is thin. In the posterior part of both lungs, there is a great deal of hemorrhagic discoloration. These areas are crepitant and of full size. It appears that some blood has infiltrated the lung parenchyma itself. On cross section in the posterior lower part of the lower lobe, there is an area which appears necrotic. The tissue tears readily and has a pale, boiled appearance. Both lower lobes have a somewhat friable appearance. None of the characteristics of pneumonia, such as infiltration or gray, granular plugging of the alveoli, is present. This may possibly be due to the absence of leucocytes from the blood stream (?).

The Spleen weighs 100 grams. It is soft and flabby, cuts with a little increased resistance. The fibrous tissue appears increased in amount. The pulp is scanty.

Fatty

The Liver weighs about 1800 grams, is very soft, has a yellowish color. The cut surface is friable. The liver markings are gone. There is no infiltration suggesting leukemia.

The Gall-Bladder has a thin wall. The lumen contains no stones. The mucosa is smooth. The ducts are not dilated or fibrosed.

Capillary hemorrhage

Gastro-Intestinal Tract. The esophagus shows only postmortem change. The stomach contains about 300 cc. of blood. The mucosa is speckled with numerous petechiae. None of these are ulcerated. The duodenum is quite red, probably stained by blood. Throughout the small bowel and particularly in the large bowel (terminal part) there is a large amount of blood. In the colon, the blood is tarry and sticky in consistence. The small bowel shows blood, more liquid. Examination of the mucosa is difficult because of the discoloration and adherence of this material. Portions are examined. In all the areas examined, there are small petechiae on the mucosa but no large ulcers are seen. The outer surface of the bowel is smooth and not covered by any fibrin or exudate.

The Pancreas is tough, appears a little large, shows no fibrosis, tumors or cysts.

Adrenals are well developed. The medulla appears a little prominent. No hemorrhage or adenomas seen.

Swollen kidneys, Pyelitis

Each of the Kidneys weigh 160 grams. The capsules strip easily. The surface is smooth. Both kidneys appear bulky, are soft and yellow. The cortex is of good size. The demarcation into cortex and pyramids is retained. The pelvis on the left side contains clear urine. The mucosa is not thickened. There is no injection. On the right side, the pelvis contains frank pus (thick, yellowish, sticky material). The pelvis on this side does not appear thickened and is not injected. The ureter is not dilated.

Bladder has thin wall. Some trabeculation. No cystitis grossly.

Prostate is soft. No inflammation. On cross section, no abscesses or fibrosis is seen. Both seminal vesicles are dilated. The walls are thin. No recent or old inflammation is seen.

Hyperplasia? of lymph nodes

Along the aorta in abdomen there are many small, reddish nodes. The largest measures about 1.5 cm. in diameter and the remainder about .5 cm. The total number of nodes is between 50 and 60. Two or three small lymph nodes similar to these are found in the gastro-hepatic ligament and 6 or 7 on each side of the hilus of the lung.

Marrow fatty

Marrow: The right femur is open from below the middle of the shaft to the upper end. The normal bone marrow is entirely gone, and is displaced by fat. It is yellow in color and apparently has no stroma. Attempts to pick it out from the marrow cavity breaks is down into goblets of fat. The material in the cancellous portion of the bone is approximately the same.

Ribs: Marrow is somewhat orange in color but still presents the same fatty characteristics. It appears to have a little more body to it than the femur.

Sternum: The marrow here is of about the same type as in the ribs.

Muscle Hemorrhage

The muscle of the left deltoid region is incised. In between the bundles of the muscle, there is a cavity holding about an ounce of thick, bloody material. The nodule in the right forearm is likewise incised. The nodule is composed of an induration within the muscle body without liquefaction or hemorrhage at this point.

Conclusions

1. Aplastic anemia.
2. Petechial hemorrhages of skin, pericardium and bowel.
3. Hemorrhage and gangrene of lung.
4. Cloudy swelling and fatty change of liver.
5. Cloudy swelling of kidneys.
6. Pyelitis, right.
7. Intramuscular hemorrhage.
8. Fatty replacement of bone marrow.

Microscopic:

Lung: marked edema, interalveolar hemorrhage (recent and old); areas of old fibrotic atelectasis 'chronic interstitial pneumonia); numerous bacteria, pus cells present in some areas.

Spleen: No significant change.

Lymph nodes: Hemorrhages in some.

Liver: Several areas of central focal necrosis.

Kidney: Albuminous precipitate in glomerular space and tubules. No glomerulitis.

Heart, pancreas, bladder, prostate, seminal vesicles, adrenals: normal.

Muscle (deltoid): Acute necrosis with purulent infiltration at edge of abscess.

Bone marrow: Smears: Adult myeloid leucocytes. Few (5 to 10%) myelocytic and myeloblastic cells. Majority of cells are undifferentiated. No megakaryocytes seen. Normoblasts and adult forms of nucleated reds rare.

Sections: Appear exactly like section of lipoma. Few cells in interspaces between fat globules.

Bacteriology:

Smears of deltoid abscess: extremely heavy flora of widely mixed organisms. Coccoid forms predominate.

Blood culture: Heavy growth of B. subtilis, staphylococci, streptococci and pneumococci. (Contamination in taking heart's blood probable.

Bone marrow (Loeffler's blood serum): Sterile after 10 days. No asserobic cultures.

IV. ABSTRACT

APLASTIC ANEMIA

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9. Carey, J. B. and Taylor, J. H. Primary aplastic anemia, a discussion and report of two cases. Ann. Int. Med. 5:471-478, (Oct.) '31.

10. Editorial; Agranulocytic Angina. J.A.M.A. 101:368-369, (July 29), '33.

There are four blood diseases in which deficient formation of myeloid elements can be demonstrated: pure red-cell anemia, idiopathic purpura (deficient platelets), agranulocytic angina (granulocytopenia), and aplastic anemia (combination of all three). Apparently none of these conditions are due to abnormal destruction of myeloid elements but are caused by their failure of development in the bone marrow.

Historical:

In this group, the purpuras, probably because of more obvious manifestations, were first described. The background dates to Werlhof (1731-1735), Hayem (1883), Kraus (1883) and Denys (1887-1889). Aplastic anemia was next described by Ehrlich (1888). In 1922, Kaznelson recorded first case of pure red-cell anemia. In same year, Werner Schultz described agranulocytic angina.

The clearest and most instructive discussions of these four diseases are those which treat all as correlated diseases of the bone marrow. In the past, these conditions have been more or less isolated into separate entities: agranulocytic angina by the laryngologists, idiopathic purpura by the surgeons and aplastic anemia by the internists. The overlapping has caused confusion and this phase has been previously reviewed (thrombocytopenic purpura: Staff Meeting, March 2, 1933). It is possible that greater clarity will result when the interest in all four conditions is focused on the common primary lesion in the bone marrow.

Aplastic Anemia:

This is a condition in which there is a progressive diminution in the formation of those elements of the blood, the erythrocyte, granulocyte and platelet, which develop in the bone marrow.

They are not produced in sufficient numbers to compensate for the natural destruction in the reticulo-endothelial system.

Cause:

On this basis, the disease may be divided into two types "idiopathic" with an undetermined cause and "secondary" with a known etiological factor. These agents are several.

(a) Benzol and (b) arsphenamine and their derivatives, whose action is often selective. Granulocytes and platelets are first attacked giving rise to symptoms of purpura and agranulocytosis. Later (and with larger doses) the red cells are involved and aplastic anemia develops. Several cases have been reported. The clinical course varies in the relative time of appearance of purpura, granulocytopenia and aplasia. At autopsy all cases show fatty aplastic bone marrow.

(c) Mustard gas. The course in the reported cases resembles benzol poisoning. Sometimes an outpouring of immature cells into the blood tides the patient over until regeneration occurs. In those that die, typical aplastic anemia (or agranulocytosis) is present and at autopsy fatty marrow is found.

(d) Irradiation by x-ray or radium. In small doses have a stimulating effect (? ours). Larger doses, "hard" rays or gamma rays of radium produce inhibition of the myeloid cells in this sequence: granulocytes, erythrocytes and lastly platelets. The condition when marked resembles typical aplastic anemia. Outbreaks in workers with radio-active elements have occurred (Orange, N. J.) (but this is entirely different as radium elements - alpha particles - are involved).

(e) Sepsis. It is said that overwhelming sepsis, malignant endocarditis, miliary tuberculosis, typhoid and diphtheria can cause aplastic anemia. This opens up a disputed subject. The terminal aplasia secondary to the diseases named above bears no resemblance to true aplastic anemia in its autopsy findings. This will be discussed under "Pathology." However, the occurrence of this condition in septic states has given rise to the theory that true aplastic anemia may be a result of focal infections. This is unwarranted by the pathological and bacteriological studies. Removal of teeth and other foci as treatment for aplastic anemia is severely criticized by some authors.

(f) Parasites. Usually the anemia following infestation by parasites is of the megaloblastic type (like in pernicious anemia), but rare cases of the aplastic form have been found.

(g) Exhaustion of the bone marrow. In pernicious and other anemias, especially the hemolytic types, and in certain diseases of the gastro-intestinal tract such as sprue, fatty and chylous diarrhea, coelic disease, pellagra and malignancy, the bone marrow becomes "exhausted" and a picture of aplastic anemia results.

(h) Myelophthisis. Tumors of bone marrow, osteosclerosis, leukemia, aleukemic leukemia may crowd out the bone marrow to the extent that "aplasia" is produced.

(i) Other causes: Other agents similar to those mentioned above have been reported: Arsenic, trinitrotoluene, bismuth, etc.

Clinical course:

The disease occurs most commonly between 15 and 30. A few cases in children and a still smaller group in older people have been reported. Females are said to be more often affected than males. Onset is insidious. There is a progressive loss of strength, breathlessness and pallor. Sometimes a vague history of poor health from childhood is obtained but usually the health previously has been excellent. There is no significant loss of weight. Physical examination is negative except for pallor. No adenopathy, splenomegaly, enlarged liver, glossitis or cord changes are

present. Urobilin in urine, increased blood pigments, achlorhydria are all absent. Late in the disease, petechiae or hemorrhages (into any organ) appear. Sepsis, usually of the naso-pharynx, is a frequent terminal feature.

The blood picture:

The red blood count is usually below a million. The cells are well filled with hemoglobin and the color index is above or near one. Immature forms are rare. Reticulocyte counts are not raised, indicating a loss of power of regeneration. This absence of all signs of regeneration is distinctive of the disease. In rare cases, there are exceptions to this rule. The fragility of the cells is said by Minot to be increased but this is not entirely accepted.

The leucocyte count is low, rarely above 2,000. 70 to 90% of these cells are lymphocytes. Granulocytes may be entirely absent. No immature cells are present. Osgood and Haskins state that the lobulations in the granulocytes are increased in numbers indicating increased age. This prolonged life cycle of the cells is thought to be a protective mechanism.

Platelets are decreased in numbers, rarely they are absent. The change in this element takes place late.

Pathology:

The significant changes are in the bone marrow. All of the marrow is transformed into yellow fat. In the cancellous bone, a few remnants of red marrow may persist. Here, the appearance of the marrow suggests pus. The organs show petechiae or hemorrhages usually into the mucous and serous surfaces. Varying degrees of septic processes may be found in organs exposed to bacteria, such as mouth, respiratory tract, rectum or vagina.

Microscopically, there are a few granulocytes in the marrow and no evidence of red blood cell formation. In the inflammatory lesions, pus may not be formed. The exudate in such cases is necrotic tissue and mononuclear cells. Hemosiderin is absent in the organs except at the site of hemorrhages. Fatty degeneration due to the anemia is present in the parenchymal organs.

Bacteriology:

A wide range of organisms have been recovered postmortem from the septic terminal processes. Exclusive of these, no significant results have been obtained. Blood cultures (prior to terminal sepsis) have been negative. Cultures of the bone marrow have been sterile except in a few instances. In these, the evidence points toward secondary and incidental infection. Chronic foci have been absent. This is in sharp contrast to the types secondary to sepsis. In these, the process is infectious from the beginning.

Agranulocytic Angina:

These cases occur with moderate frequency - over 500 cases have been reported in recent years. More accurate diagnosis will show a greater incidence than has been noted in the past.

Clinical course:

The illness occurs most frequently in middle-aged individuals but no age is exempt. 70% have been in males (Lescher). Jackson in his 69 cases had 87% females. The onset is abrupt and comes on in persons apparently in good health. There is fever, malaise, general prostration and ulcerative and necrotic stomatitis or pharyngitis. Jaundice has been described in about 50% and is said to be due to a hepatitis (enlarged tender liver). The spleen is sometimes enlarged. There is no lymphadenopathy and no petechiae or hemorrhages. The disease runs a rapid, short and often fatal course. The duration in acute cases is from 4 to 8 days and death is due to sepsis and bronchopneumonia. There is great variability in the symptoms and signs. Numerous cases are now on record in which death did not take place. (See results of treatment below).

The blood picture:

is highly characteristic. The red cells, hemoglobin and platelets are normal. There is a rapidly progressive diminution in the granulocytes. The total count may fall as low as 100 and in fatal cases is always below 2,000. The granulocytes may entirely disappear.

Pathology:

"Grossly, the bone marrow appears normal. A liquified appearance is described. Microscopically, however, there is absence of the granular cells. In these cases, the absence of "pus" cells about areas of sepsis is extremely marked. In cases which improve, the development of abscesses is a favorable sign.

Etiology:

It has been shown in several cases that the blood changes precede the onset of symptoms. The onset of the stomatitis and systemic reaction has been described as the "breaking of the clinical storm." One patient had recovered from a typical attack and blood counts were made daily. The count had returned to normal. About $3\frac{1}{2}$ months after recovery, the neutrophiles began to disappear. In 3 days, they were absent. On the fourth day, the onset of clinical symptoms occurred and in four more days, the patient was dead.

Biopsies of bone marrow during life have shown that the depletion of neutrophiles is not a terminal condition. There apparently is a failure of development in the marrow. The conclusion drawn from these observations is that "it is now well-established that the agranulocytosis is due to deficient production of granulocytes in the bone-marrow and not in the circulation." (Lescher). The stomatitis and other septic processes are secondary to the lack of granulocytes.

The cause of agranulocytosis is unknown. Septic states produce excessive destruction of the cells but the infectious lesions are present first and the diminution of the granulocytes progresses as the infectious disease advances. The conclusion drawn is that in typical agranulocytic angina, there is a primary hypoplasia of the marrow in which the actual cause is unknown. (Compare, Dennis, E. W. cited below).

Idiopathic Purpura Hemorrhagica.

In a previous staff meeting, the current views regarding this disease were reviewed. (4:239-245, March 2, '33). At that time, it was emphasized that the typical "essential" thrombocytoperic purpura is becoming less and less a clear-cut entity. Associated features of agranulocytosis and aplastic anemia are being found. In addition, symptomatic purpura and infectious vascular dysfunctions were found to comprise a considerable percentage of the cases. Certain cases of true "idiopathic" purpura, however, do occur. It was concluded that there was no evidence of increased destruction of platelets. Failure of production in the bone-marrow was considered to be the essential lesion. A summary of these discussions may be made as follows. There is a wide group of purpuras. Most of these are symptomatic and associated with widely separated primary diseases. There is another group associated with agranulocytosis and aplastic anemia. Finally, there is a small group of pure thrombocytopenic purpura. The diminution of platelets is due to a failure of development in the bone marrow.

Red-cell Anemia:

The fourth group of cases in this set of myeloid deficiencies is rare. Only 3 cases are on record. The characteristic blood count is as follows: erythrocytes, 552,000; hemoglobin, 12%; color index, 1.07; leucocytes, 4,980; differential count, normal; blood-platelets, 207,000.

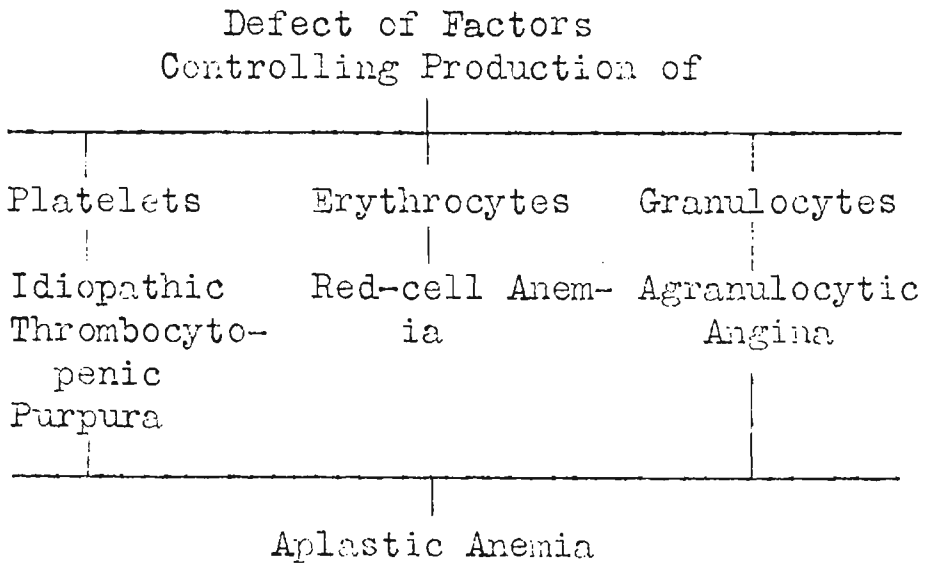
This group becomes of interest when attempts are made to correlate the various dyscrasias. It is thought that this disease represents suppression of only the red cells in the marrow.

Correlation of Aplastic Anemia with Agranulocytosis, Idiopathic Purpura and Red-Cell Anemia.

Lescher and Hubble have attempted the correlation of these diseases upon a throty of bone marrow hypoplasia. The following is taken almost verbatim from their article.

If the bone marrow without obvious cause suddenly diminishes the output of certain cells, it is natural that the reason be sought in the failure of the mechanism which controls the output of these cells. Clear-cut individual types and intermediate forms of cell deficiencies occur. The selective agent causing the deficiency apparently is not rigidly specific. The nature of this agent is indefinite. Absence of certain food substances, lack of some vitamin, lack of certain metals, and disturbances of endocrine secretions have been proposed.

The theory may be summarized as follows: There is a controlling mechanism for the production of each myeloid element. A disturbance of this mechanism produces a specific blood dyscrasia. Combinations in this disturbance may be present giving rise to mixed forms of dyscrasias. This may be put into diagrammatic form:



Arsphenamine and Bone Marrow:

It is well-known that the arsenicals may produce various blood dyscrasias. McCarthy and Wilson have collected all the reported cases. A total of 79 were found. They are not common because in one series of 78,350 injections with 338 complications only 2 cases of anemia were found. These authors classify the types of blood dyscrasias as follows:

		Died	Mortality
Thrombocytopenia	12	0	0
Thrombocytopenia and granulocytopenia	7	1	14%
Agranulocytosis or granulocytopenia	12	4	33%
Aplastic anemia	34	28	83%

In general, the clinical features and the prognosis resemble that of the idiopathic forms of these illnesses. It is of great interest that the identical causative factor (arsphenamine) can produce any one of the 3 main types of blood dyscrasias which Lescher and Hubble have attempted to put together into one pathogenetic group. The 2 studies apparently were done independently at the same time.

Differential Diagnosis of Aplastic Anemia.

(a) From Pernicious Anemia.

Typical cases of either disease can hardly be confused. However, in pernicious anemia, in the rapidly fulminating cases and in those inadequately treated, a stage resembling aplastic anemia can appear. Even at autopsy, the distinction may be difficult. The diagnostic points in these atypical pernicious anemias which usually can be found are: evidences of regeneration in the red cells, increased bile pigments in the blood or urine, cord changes, achlorhydria and at autopsy, hemosiderin in the tissues and evidences of hyperplastic (may be only focal) bone marrow. In some cases, the distinction may be very difficult.

(b) From Chronic Hemolytic Anemia.

Increased fragility and increased bile pigments combined with normal platelets and granulocytes usually differentiates these conditions.

(c) From Aleukemic Leukemia.

This disease can imitate aplastic anemia to perfection. All the findings may be present in the clinical study. Only at autopsy does the leukemic infiltration of the bone marrow and viscera reveal the true nature. The number of such cases is increasing. The differential points may be accidental findings. A blood study at a stage when immature white cells or an elevated white count is present is almost the only distinguishing point. The aplasia in these cases appears to be due to crowding out of the normal bone marrow by leukemic infiltration. An occasional case of chloroma may produce the same picture.

(d) From Idiopathic Purpura and Agranulocytosis.

Lescher and Hubble, as stated before, believe these are related processes. The three diseases frequently are mixed. In pure thrombocytopenic purpura, the platelets alone are involved. Bleeding may cause anemia but many evidences of regeneration are present. In pure agranulocytosis, the red count and platelets are normal at the onset. The usual order of suppression in aplastic anemia is erythrocytes, granulocytes and finally platelets. However, the platelets may disappear first and for a time the picture of purpura is present. If the granulocytes are affected first, agranulocytopennia may be imitated. The true nature becomes manifest later in the course.

Osgood and Haskins give the following data as characteristic of aplastic anemia.

	Normal	Aplastic Anemia
Color index	.7 - 1.2	.8 - 1.2
Rbc (1,000,000)	4.4 - 6.4	.8 - 4.0
Hbg. (grams)	13.5 - 19.0	2.0 - 12.0
Cell volume per 100 cc.	38.0 - 50.0	6.0 - 35.0
Anisocytosis	0	0 - +
Poikilocytosis	0	0 - +
Polychromatophilia	0	0
Reticulocytes (%)	0 - 1.0	0
Normoblasts	0	0
Megaloblasts	0	0
Fragility begins	.46 - .42	.46 - .42
Fragility ends	.36 - .30	.36 - .30
Icteric index	4.0 - 6.0	.5 -15.0
Urobilinogin in urine (dilution in which +)	0 to + in .1	0 to + in .5
Urobilinogen in stool	2+	+
Wbc (1,000)	5.0 - 10.0	.1 - 3.0
Pmn	55.0 - 75.0	0 - 20.0
Small Lymph	20.0 - 35.0	80.0 -100.0
Eosinophiles	1.0 - 4.0	0 - 1.0
Immature cells	0	0

Prognosis:

The idiopathic types of aplastic anemia appear to be almost hopeless. Lescher and Hubble could find only 5 cases in which treatment was of any material benefit. They reported one more such case. In the secondary types after arsphenamine, McCarthy and Wilson found a mortality of 83%.

Treatment:

In the idiopathic forms, numerous treatments have been tried. Iron, arsenic, removal of foci and liver therapy have proven of no benefit. Repeated transfusions appear to help. Lescher and Hubble review one case who received a total of 105 transfusions. (Since this paper, other such cases have been reported).

Adrenalin: is recommended. It was used in 2 of the 6 cases which improved.

Splenectomy: One brief mention of improvement after this operation was found. No discussion was given.

Nucleotides:

Through the work of Jackson, the use of nucleotides has become almost specific for agranulocytic angina. In 1924, Jackson demonstrated pentose nucleotide in normal blood. In 1931 (April), he and his co-workers reported a temporary improvement in a myeloblastic leukemia from the use of nucleotide.

In 1931 (November), they reported the results of treatment in 20 cases of granulocytopenia. 14 of these recovered. In 1932, they reviewed the results of 69 cases. These cases consisted of 54 typical agranulocytic anginas, 13 cases secondary to sepsis and 2 cases of benzol poisoning. The average duration of the illness was 7.2 days. 48% had wbc's below 1000, 15% below 500 and 55% showed complete absence of pmn's. The treatment recommended consisted of injections of nucleotide (K 96). (Smith, Kline and French Lab., Phil.) (This is now available as a sodium salt of pentose nucleotide called "pentnucleotide.") 10 cc. doses by intramuscular injection are given twice daily until a rise in white blood count occurs. Then 10 cc. once a day is given for 3 days and thereafter the patient is watched for recurrence. In critically ill cases, a "vial" (number of cc. not stated in the article) diluted in 100 cc. of saline is given intravenously each day in the morning and 10 cc. is given intramuscularly in the evening for 4 days. Then the treatment is continued with bidaily intramuscular injections until improvement begins and following this daily injections for 3 more days. Improvement takes place almost constantly on the 5th day. In the meantime, the patient may appear to be worse but the treatment should not be discontinued. Occasional nausea and dyspnea, rarely chills and fever occur. No other treatment except nursing care and high fluid intake is given.

The results may be summarized as follows:

	Number	Mortality %
Untreated	--	90
Miscellaneous treatment	178	74
Arsphenamine	33	72
Blood transfusion	53	64
Irradiation	64	53
Nucleotide	69	26

In the 69 cases, 54 had typical angina and 70% of these recovered. There were 17% (9 cases) with recurrences and 2 of these 9 died. In 13 cases due to sepsis, 11 recovered (84%). In the 2 benzol poisonings, both recovered.

In 33 cases with a leucocyte count below 1000, 66% recovered. In 10 cases with a count below 500, 70% recovered. These cases were treated by 40 physicians in 12 different states. In aplastic anemia: no report of the use of nucleotide in aplastic anemia was found. The excellent results obtained in agranulocytic angina, however, supports the view of Lescher and Hubble that a specific agent is absent which disturbs the control of granulocyte production. If the various conditions described are of the same nature, nucleotide may improve cases of aplastic anemia. It suggests, at least, that some specific (?) body may be also found for this illness.

Experimental Agranulocytic Angina:

Ref: Editorial: Experimental Agranulocytic Angina,
J.A.M.A. 101:368-369 (July 29) '33.
Original: Dennis, E. W.,
J. Exper. Med. 57:993 (June) '33.

Dennis observed that several of the organisms associated with agranulocytosis were capable of producing leukocidins in culture media. The previous experimental work had dealt only with the effects of generalized infections with these agents. He, therefore, placed cultures of various organisms in sealed parchment sacs and introduced them into the peritoneal cavities of rabbits. The symptom complex produced simulated agranulocytosis in man. With S. viridans, a fulminating type was produced with granulopenia within a few hours and death usually within 24 hours. Disintegration of granulocytes in the blood began almost immediately. Staphylococcus aureus produced a slower type of the disease. When the organisms escaped from the capsule, there resulted an increase of leucocytes in the blood stream. The author concludes that the constant absorbtion of toxin without actual influx of organisms produced the granulocytopenia. He states "these conditions are satisfied in a chronic (or encapsulated) focal infection in man."

Summary:

1. Attempts are being made to draw primary agranulocytic angina, essential thrombocytopenic purpura, red-cell anemia and aplastic anemia into the same caregory: primary bone-marrow deficiencies.

2. The clearest discussions of these cases are those which take this attitude.

3. Several causes of secondary aplastic anemia are known. Of these, benzol, arsphenamine, and irradiation produce a condition very similar to true aplastic anemia in all its forms.

4. Septic states result in a similar blood picture but the course and autopsy findings are not like those of aplastic anemia.

5. Displacements (tumor, leukemia) of bone-marrow and exhaustions as in pernicious anemia may resemble aplastic anemia perfectly.

6. The onset is insidious and the symptoms are those of anemia. The physical examination is negative.

7. The blood picture is that of aplasia. There is no evidence of regeneration or increased destruction. The aplasia involves all elements of the bone-marrow. The changes are progressive.

8. At autopsy, fatty replacement of the bone-marrow with no hyperplasia and without evidence of increased destruction in the viscera is found.

9. Bacteriological studies are negative. (See below regarding granulocytopenia).

10. Agranulocytic angina (idiopathic) is thought to be a related condition. There is failure of development of granulocytes. This precedes the clinical manifestations. The cause is unknown.

11. True idiopathic thrombocytopenic purpura is considered to be a similar bone-marrow deficiency disease in which platelets are suppressed.

12. Red-cell anemia while rare is said to represent suppression of the erythrocytes.

13. On the basis of these four types of selective suppression of myeloid cells, the theory is advanced that each represents a disturbance in the growth control of that specific cell. Mixed forms are frequent and aplastic anemia represents the combined process involving all elements.

14. Something of this same idea is suggested in the bone-marrow reactions to arsphenamine. In 79 cases, each of the 3 main types are represented. Arsphenamine alone may act as the disturbing agent to any one or all 3 of the myeloid elements.

15. In the differential diagnosis, emphasis is laid on the absence of all regenerative phenomena and on absence of signs of hemolysis of blood. In some cases, particularly in aleukemia, the postmortem examination (or bone-marrow biopsy) is necessary for diagnosis.

16. The prognosis for aplastic anemia is very poor.

17. The treatment is not standardized and appears to be of little help. Transfusions and adrenalin are recommended.

18. Pentnucleotide appears to be of great benefit in the treatment of agramulocytic angina. The mortality is reduced to 26%. The results suggest that the absence of specific substance is causing the disease.

19. This supports the theory that all four conditions are due to interference with the normal growth control of the various myeloid elements.

20. In contrast to the non-bacterial theories of etiology evidence (Dennis) is presented to show that pyogenic bacteria are capable or producing granulocytopenia when they are restrained from active penetration into the tissues by enclosing them in a parchment sac. The constant supply of the toxin (in

contrast to an injection) induces the depression of granulocytes. It is suggested that focal or encapsulated infections reproduce these conditions in humans.

Abstr. Rudolph Krucky.

V.

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REPORTS BY

DIVISION OF DIAGNOSTIC RADIOLOGY

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