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Agammaglobulinemia

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Editor

Robert B. Howard, M.D.

Associate Editors

William D. Armstrong, M.D.
William F. Maloney, M.D.
Erling S. Platou, M.D.

Richard L. Varco, M.D.
W. Lane Williams, Ph.D.

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Address communications to: Staff Bulletin, 1342 Mayo Memorial, University of Minnesota, Minneapolis 14, Minn.

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G R E E T I N G S

Once again we are inaugurating the weekly staff meetings of our University of Minnesota Hospitals. This is always a thrilling occasion but the meeting this year in our new auditorium is something very special.

For fifteen years we have dreamed about and for more than ten years have been actually planning for the Mayo Memorial. To be moved in and to have it in use seems more like a dream than reality. Yet here it is; we can see it, touch it and use it. Truly this is a memorable occasion for all of us.

In this new building as well as in the remodelled and refurnished older hospital we have splendid facilities and new equipment for our work. The public has provided all this, in part through taxes, and in part through voluntary contributions. In accepting it we assume a very real obligation to do more and better work in teaching, in research and in the care of patients.

The training of physicians, nurses, public health specialists, medical and x-ray technicians, physical therapists, occupational therapists and other medical and health personnel is our first responsibility. The new building provides us with better facilities for such teaching than we have ever had before. Let us use them effectively and make good teaching our first concern.

Research is the foundation of medical progress and the spirit of vital and stimulating teaching. Our Medical School is already a leader in research. The new facilities, although still inadequate in certain areas, will greatly facilitate more effective research; research which is certain to make important contributions to medical knowledge and to give us more effective tools for the prevention and treatment of disease.

And finally, we have patient care, the object of both teaching and research. It is mentioned here last but it really comes first in importance. The best of medical service and personal, kindly consideration of each and every patient is what we strive for above all else. The new building and equipment provide us better facilities for the care of patients and I am sure that the best of medical care will be the result. Let us just be careful not to lose sight of the patient as an individual in all of this.

So, on the occasion of this first Hospital Staff Meeting, I extend to all members of the staff - old and new alike - warmest greetings and best wishes at the beginning of what I am sure will be a new era of progress and achievement for our Medical School and University Hospitals.

Harold S. Diehl, Dean

I. AGAMMAGLOBULINEMIA--A Provocative Experiment of Nature^{+ ‡}

Robert A. Good, M.D.^{/ ‡}

Absence or virtual absence of gamma globulin as determined by electrophoretic analysis of the serum protein has been recognized for several years as a concomitant of a number of diseases. In the nephrotic syndrome, for example, hypogammaglobulinemia and hypoalbuminemia occur reflecting the loss of these two protein components in the urine.¹ Patients with nephrosis are not lacking in capacity to synthesize protein. Indeed, Kelley, Ziegler and McQuarrie² showed that increased rather than decreased protein production occurs in this disease. Hypogammaglobulinemia and perhaps even agammaglobulinemia occur also as part of a disease originally observed by McQuarrie³ and later studied by Schick⁴ in which there seemed to be a symmetrical failure of protein fabrication presumably as a function of hepatic inadequacy. Recently Fried and Henley⁵ studied such a case and again emphasized the deficiency of circulating gamma globulin in these patients. Hypogammaglobulinemia along with generalized hypoproteinemia is sometimes a function of excessively rapid destruction of serum proteins as in the patients studied by Dixon⁶.

In each of the above disorders, depression of gamma globulin concentration occurs in the plasma or serum but is associated with a disturbance in metabolism of other serum protein components.

In 1952 Col. Bruton^{7,8} described a disease entity expressed clinically as an inordinate susceptibility to bacterial infection. Electrophoretic studies revealed that this disease was featured by complete absence of gamma globulin from the serum. Bruton's patient, an 11 year old boy, was shown to be lacking in circulating antibodies and to be unable to produce antibodies in response to anti-stimulation. Unlike the instances of agammaglobulinemia previously described, electrophoretic analysis of the plasma or serum from this patient revealed a protein partition essentially normal except for the absence of gamma globulin. Following Bruton's case report, Janeway, et al⁹ gathered together nine such cases. Each of the latter group exhibited the cardinal features described by Bruton, namely:

1. increased susceptibility to bacterial disease
2. absence of gamma globulin in the serum
3. absence of circulating antibody in the blood and tissues
4. failure of antibody production in response to antigenic stimulation.

The studies of the Boston group established that agammaglobulinemia is due to failure of synthesis of this particular electrophoretic component of the serum proteins and is not a function of generalized protein dysmetabolism. Further, it was established that this type of agammaglobulinemia is not due to inordinately rapid decay of gamma globulin. For example, parenterally administered gamma globulin had, in these patients, a half life essentially the same as that de-

⁺ From the Laboratories of the Variety Club Heart Hospital and the Department of Pediatrics, University of Minnesota Medical School, Minneapolis 14, Minnesota.

[‡] Aided by research grants from the Helen Hay Whitney Foundation, U. S. Public Health Service RG 2990, Minnesota Heart Association, American Heart Association and the University of Minnesota Graduate Research Fund.

[/] A number of the studies referred to were done in cooperation with Dr. Richard L. Varco and will be published in detail elsewhere.

[‡] The author is deeply indebted to Mrs. Ursula Brunner, Mrs. Janet Brodahl and Miss Donna Jensen for technical assistance and to Dr. I. McQuarrie and Dr. L. Thomas for stimulating advice.

scribed by others¹⁰ for normal human subjects. During the past two years electrophoretic analysis of the serum of patients showing increased susceptibility to bacterial infection has turned up many instances of agammaglobulinemia (approximately 30 such cases are known to the present author).

Almost every laboratory in a medical center having both a large patient load and an electrophoresis apparatus has turned up at least one such case. Patients with this disease are regularly severely and recurrently ill because they lack one of the established mechanisms of defense against infection. From such preliminary data as are available it appears that there are at least two separate clinical forms of isolated agammaglobulinemia.

The form described by Bruton seems to be a congenital disease representing an inborn error of metabolism transmitted as a sex-linked recessive trait. This type of anomaly of protein synthesis has its prototype in hemophilia. The latter disease too is an inborn error of protein formation resulting in the absence of a particular protein component from the blood. As with agammaglobulinemia, hemophilia is transmitted as a sex-linked recessive factor. Somewhat similarly, with respect to fibrinogen,¹¹ a hereditary hemorrhagic diathesis has been discovered which is due to the complete absence of a particular protein component (namely fibrinogen) from the circulating blood. The latter syndrome referred to as afibrinogenemia has been intensely investigated by Frick and McQuarrie.¹² The form of agammaglobulinemia occurring in children is, then, sex-linked, congenital and familial. Whether congenital agammaglobulinemia requires further subdivision must be decided upon future study. The possibility that this is true is suggested by our data.

In addition to and distinct from this group of patients, agammaglobulinemia has been found to exist in adults. As in the childhood disease, agammaglobulinemia in adults is expressed clinically as a marked decrease in re-

sistance to bacterial infection. The latter form of agammaglobulinemia appears to begin at any age in either sex and clinical evidence indicates that it is an acquired disease. Preliminary studies suggest also that delicate quantitative immunological methods may separate agammaglobulinemia as diagnosed electrophoretically into true agammaglobulinemia (actual absence of this component from the serum) and extreme hypogammaglobulinemia.¹³ Congenital agammaglobulinemia is usually complete while the adult disease is really an extreme hypogammaglobulinemia. Further evidence for such classification will be presented in this report. Electrophoretically both diseases are expressed as an absence of detectable gamma globulin in the serum or plasma.

During the past nine months we have discovered and studied seven patients having agammaglobulinemia revealed electrophoretically as an isolated disturbance of protein synthesis. Five of these patients are children representing three families and two are adults. The children are all boys. One adult is female and the other male. Each of the patients suffered from an illness featured by recurrent severe bacterial infections. Three of the children and both of the adults have been subjected to intensive clinical, hematological, pathological and immunological investigation in an attempt to elucidate the nature of the handicap, to define in these patients the relationship of the congenital to the acquired disease and to make inquiry into a number of fundamental immunological problems to which an incisive approach is offered by the revealing experiment of nature.

In Table I are summarized the results of analysis of the serum proteins from these patients according to standard methods. Fractionation of the albumin and globulin was performed with 26% sodium sulfate. The zinc turbidity determination was performed according to the method of Kunkel.¹⁴ As may be seen in the Table, the total protein concentration in these patients was uniformly low or at the lower limits of normal. The albumin concentration was, however, regularly within the normal range and the slight

TABLE I

Serum Proteins in Agammaglobulinemia

Patient	Age	Total Protein	Albumin	Globulin	A-G Ratio	Zinc Turbidity
.	7 yr.	5.7	4.2	1.5	2.80	0 units
.	7 yr.	5.5	3.5	2.0	1.75	0 units
.	6 mo.	5.5	4.0	1.5	2.66	0 units
.	20 mo.	5.5	2.5	3.0	0.83	---
.	15 mo.	5.7	3.2	2.5	1.28	---
.	58 yr.	5.4	3.5	1.9	1.84	0 units
.	26 yr.	6.2	4.6	1.6	2.87	0 units

depression of total serum protein observed was attributable to a deficiency of circulating globulin. The result of this protein distribution was an increased albumin-globulin ratio, a distinctly unusual finding in patients presenting, as these patients did, with a history of chronic or recurrent infection. The zinc turbidity test performed many times in these patients

showed either no turbidity or an insignificant reaction (0-1 unit). Normal values for gamma globulin precipitated in this way is 5 to 6 units in children and range from 2 to 13 units. Electrophoretic analysis of the serum proteins (Table II) in most of the patients revealed essentially normal values for each of the components save gamma globulin. Just as in normal persons, however,

TABLE II

Electrophoretic Analysis of the Serum Proteins in Patients with Agammaglobulinemia

Patient	Protein Fraction gm%					Total Serum Protein
	Albumin	Alpha 1 Globulin	Alpha 2 Globulin	Beta Globulin	Gamma Globulin	
.	4.20	0.29	0.69	0.82	0.00	6.0
.	3.68	0.65	0.38	0.78	0.00	5.5
.	4.55	0.38	0.23	0.33	0.00	5.5
.	2.85	0.72	0.99	0.84	0.00	5.4
.	3.86	0.66	0.76	0.92	0.00	6.2
.	3.44	0.96	0.79	0.27	0.03	5.5
.	2.29	1.19	1.19	1.02	0.00	5.7

during severe infections, elevations of alpha globulin were noted in several instances. On electrophoretic analysis the gamma fraction was completely absent in each case. It is on the basis of the electrophoretic patterns from each patient (Figure 1) that the diagnosis of agammaglobulinemia was made.

In Table III are summarized the results of complete liver function tests performed in 5 of the 7 patients. No significant deviation from normal values was found with the exception of a low concentration of globulin and the decreased zinc turbidity reaction. Even the most delicate indices of hepatic adequacy, the bromsulphthalein retention

TABLE III
Studies of Liver Function in Patients with Agammaglobulinemia

Patient	Serum bilirubin		C.C.	T.T.	Cholesterol mg%	Cholesterol esters Mg %	U.U. mg/d	Cholinesterase Δ pH/hr.	B.S.P.
	l ¹ mg%	total mg%							
.	0.1	0.4	0	0	108	70	0.8	0.74	1%
.	0.3	0.4	0	1	---	--	trace	0.81	1%
.	0.1	0.3	0	0	---	--	0.4	0.45	1%
.	0.1	0.4	0	0	212	160	---	0.61	0%
.	0.1	0.4	0	0	---	---	0.4	---	0%

test and the 24-hour urine urobilinogen excretion fell within normal limits. Another observation, to be reported in detail elsewhere, was that liver biopsy on one of the adults and post mortem examination of the liver in one of the children revealed no abnormalities in the morphology, organization or tinctorial properties of the hepatic parenchyma. These observations, indicating an intact morphology and physiological function of the liver, must be interpreted as support for the concept that isolated failure of gamma globulin synthesis is not attributable to hepatic malfunction per se. As corollary to this conclusion must also be the recognition that gamma globulin and antibody formation probably occur at some extra-hepatic site.

A detailed study of the coagulation mechanism was carried out in 4 of these patients. This was done in an effort to exclude the concomitant occurrence of a deficiency of proteins other than gamma globulin which might be reflected in an anomaly of coagulation. The observation of normal values for each of the systematically arranged coagulation tests supports the concept formulated on the basis of data obtained by electrophoretic and chemical fractionation of the serum proteins that in this disease there exists a deficiency in the synthesis of only one protein component. Further, this study provides substantial evidence that none of the factors involved in clotting of blood is a gamma globulin.

Summarizing to this point, we are reporting 5 children suffering from the congenital form of agammaglobulinemia and two adults having the acquired form of this disease. In each instance the syndrome presented itself as an extreme susceptibility to bacterial infection beginning in the children during the second half of the first year of life following loss of passively transferred maternal gamma globulin. The value of the clinical history in establishing the diagnosis of agammaglobulinemia is attested by the fact that in the two latest cases studied, the diagnosis offered by the admitting house officer was agammaglobulinemia.

Routine laboratory studies may reflect the presence of infection or may reveal an underlying leukocytic disturbance. In several instances the routine workup was entirely negative. Studies of the serum proteins by standard methods reveal an abnormally low total protein concentration, normal albumin, low globulin, and consequently an increased A-G ratio. The zinc turbidity test was found to be a good screening test for this disease since the values obtained were abnormally low. For this reason, screening with zinc turbidity reaction permits a presumptive laboratory diagnosis of agammaglobulinemia. This latter finding is the more remarkable clinically since patients suffering, as these patients do, from recurrent or chronic infection usually show a distinctly elevated zinc turbidity reaction.

Demonstration of the Immunologic Paralysis - In an attempt to determine whether the agammaglobulinemia observed in these patients was associated with failure of the immune mechanism, a six phase study was conducted. This investigation included the following parts:

1. A search for evidence of antibody formation to antigens known commonly to stimulate normal persons was carried out.
2. Attempt was made to induce antibody production by stimulation with potent bacterial antigens.
3. Study of the so-called natural antibodies was made. This consisted of measurement of the capacity of the serum of these patients to agglutinate heterologous blood group cells, and comparison of this capacity to that of normal children.
4. Attempt was made to stimulate formation of isoagglutinins vs. heterologous blood group substances by parenteral injection of "mismatched" cells.
5. Measurement of the antibody response of these patients to a variety of potent virus antigens was performed.

The response obtained was compared to that of normal persons.

6. A study of the skin reactivity of patients with agammaglobulinemia to tuberculin, pneumococcal products and streptococcal products was conducted.

The observations appear to establish that all of the patients suffer a profound immunological handicap. Three of the children and one of the adults with agammaglobulinemia have a virtually complete "immunological paralysis". This statement is supported by the observation that no evidence whatever of responsiveness to antigenic stimuli was obtained. The other adult and two of the children, F.T. and T.T., must be classified, on the basis of present data, as having a profound "immunological paresis". In the adult, F.H., a 58 year old male who has been studied thoroughly, the only evidence of antibody formation discovered was the occurrence in his serum of a low titer of antibody against the heterologous blood group cells. In addition, a questionable increase in titer occurred on stimulation with group A cells. The situation with F.T. and T.T. cannot be evaluated clearly since their disease was diagnosed in retrospect following the death of both children and studies of immunological responsiveness were not performed. The fact, however, that an initial blood sample showed a significant isoagglutinin titer in each of these two children suggests that some immunological responsiveness was present in these representatives of the congenital syndrome.

In Table IV are summarized results of a survey conducted to find evidence of antibody formation by observation of skin or serological reactivity to antigens commonly providing stimulation in the environment of normal persons. Each of the agammaglobulinemic patients reacted positively to skin testing with Schick and Dick toxins indicating an absence of tissue antibodies against these ubiquitous antigens. Further, none of them possessed significant amounts of antibody against streptolysin, streptococcal hyaluronidase, or streptococcal desoxyribonuclease. Almost everyone has had at least one streptococcal infection by the

TABLE IV

Immunological Studies in Patients with Agammaglobulinemia

Immunological Determinations	Patient						
	E.S.	L.L.	W.A.	T.A.	F.H.	F.T.	T.T.
Shick test	+	+	+	-*	+	+	+
Dick test	+	+	+	-*	+	X	X
ASO titer	0	0	0	0	0	0	0
Streptococcal antihyaluronidase	0	0	0	0	0	0	0
Streptococcal antidesoxyribose-nuclease	0	0	0	X	0	X	X
Heterophile antibody	0	0	0	0	0	0	0
Cold agglutinins	0	0	0	0	0	0	0
Febrile agglutinins [‡]	0	0	0	0	0	0	0
Mumps C.F.	0	0	0	0	0	0	0
Herpes neutralizations	0	0	0	0	0	0	0

*at 3 months of age - negative results attributed to passively transferred maternal antibody.

X - not done

[‡]typhoid H, O, and Paratyphoid B, Proteus Ox₂, o x 19, brucella, tularemia

time he has reached his 7th year¹⁵ and as a consequence almost everyone has detectable antibody against these streptococcal antigens. That this is not so with the agammaglobulinemic patients is a reflection of their immunological handicap. In addition, Forsman antibody, cold agglutinins and complement fixing and virus neutralizing antibodies, commonly found in the serum of normal patients, were lacking in these patients. Finally, isoagglutinins vs. heterologous blood group cells were completely absent in the serums of four of the patients and present in extremely low titer in the other three.

Our interpretation of these data is that they establish in each of these patients the existence of an immunological handicap and serve as presumptive evidence of an "immunological paralysis" in four of them.

An attempt was made to provoke an antibody response in five patients with agammaglobulinemia by the injection of potent bacterial antigens. Each patient was given, at different times, a course of immunizations against typhoid and paratyphoid organisms, pneumococcal polysaccharide, and commercial DPT vaccine. At suitable intervals, following antigenic stimulation, blood samples were drawn and

appropriate tests for antibody formation carried out. Whereas control subjects responded regularly and vigorously to these antigenic stimuli, none of the 5 patients with agammaglobulinemia exhibited an antibody response. Subsequent attempts to induce antibody formation by secondary antigenic stimulation (anamnestic response) likewise failed. Electrophoretic and turbidimetric analysis of blood samples taken serially throughout the period of antigenic stimulation and for several weeks thereafter revealed no evidence of gamma globulin accumulation.

On Table V are summarized results of study of the titers of isoagglutinins against heterologous blood cells in agammaglobulinemic and normal persons. Four of our patients were of blood group O. Behaving normally, each would be expected to possess antibodies against both A and B cells. Instead, none of the four possessed antibody against either antigen. The other three patients, one adult and two infant siblings, were of blood group A and if normal, would be expected to have a high titer of antibody vs. B cells and no titer vs. A cells. In each of these patients a

TABLE V

Blood Group and Reaction to Heterologous Blood Group Cells in Patients with Agammaglobulinemia

Patient	Blood Group	Isoagglutinin Titer	
		Anti A	Anti B
	O	no titer	no titer
	O	"	"
	O	"	"
	O	"	"
	A	-	+ in 1-2 dilution
	A	-	+ in 1-5 dilution
	A	-	+ in 1-5 dilution
Normal Group O 20 cases	O	1:343.0	-
Normal Group A 18 cases	A	-	1:179.6
Normal Group B 5 cases	B	1:139.3	-

very low but definite concentration of isoagglutinin against B cells was observed. In no instance, however, did the concentration of isoagglutinin overlap the lowest normal readings obtained in our laboratory. Included for comparison are the geometric mean titers obtained on groups of patients

representing O, A, and B blood groups.

To further test the immunological handicap in agammaglobulinemic patients, an attempt was made to immunize 5 of them to heterologous blood group cells by the parenteral injection of washed heterologous cell concentrates. Mismatched cells

were injected subcutaneously, intramuscularly and intravenously in varying amounts. In no instance was any systemic reaction produced by the injection of these cells and in no instance was clear evidence of antibody production in response to this antigenic challenge observed. In the adult male of group A who showed a low but consistent microscopic agglutination of group B cells on microscopic examination of the 1/2 dilution preparation, a questionable rise of one tube (to 1/4 concentration) was recorded 10 days following injection of mismatched cells. This finding supports the conclusion drawn from preceding data that the immunological paralysis in this individual was incomplete.

It has been observed repeatedly that the sequence of clinical diseases which threaten the life of patients with agammaglobulinemia have their basis in bacterial infection. Repeated attacks of pneumococcal pneumonia, bacterial meningitis, bacterial infections of the middle ear, paranasal sinuses and of the urinary and gastrointestinal tract were regularly observed. Strangely enough, virus infections appear to be handled efficiently and normally by these patients. Study of our cases supports the observation that in spite of the immunological handicap, virus infections do not occur repeatedly and are not unusually severe. Chickenpox, poliomyelitis, mumps and measles all have been observed in our cases. In each instance the disease has run an essentially normal course and recovery has occurred in the usual fashion. The severe necrotizing reactions following injection of vaccinia virus in patients presumed to have an immunological handicap have served to dissuade us from vaccinating our agammaglobulinemic patients. However, others have vaccinated children with agammaglobulinemia. Janeway reported apparently successful uncomplicated vaccination of six cases and two of our children have been vaccinated by other physicians without untoward event. In one of our patients, three attempts at vaccination resulted in no response whatever. Whether this latter result expresses inadequacy of the vaccine administered

or lack of reactive capacity of the host has not been determined and requires further study.

In an attempt to make sense of the paradoxical behavior of agammaglobulinemic patients toward antigenic stimulation on the one hand and virus infections on the other, and to determine whether the immunological handicap of the patients with agammaglobulinemia includes failure to respond to virus and rickettsial antigens, intensive stimulation was provided with influenza, poliomyelitis, mumps, spotted fever, Q fever, typhus and W.E.E. antigens. If we explain the initial presence of low concentration of hemagglutination inhibitor against influenza virus as a reflection of the natural non-specific hemagglutination inhibitors of Ginsberg, et al, no antibody was found and no antibody response occurred after injection of any of the virus antigens. Neither primary nor secondary stimulation with mumps virus resulted in specific antibody production. These data are interpreted as further evidence of the immunological handicap characteristic of these patients. Coupled with clinical observations they must also be interpreted as evidence that anaphylactic type antibody is not essential for characteristic symptomatology of virus diseases and that recovery from virus infection may be accomplished without the aid of antibody. Clinical evidence taken together with these observations would also suggest that reinfection with virus agents may, indeed, be inhibited by means other than circulating antibody.

In Table VI are summarized data obtained in an attempt to determine whether patients with agammaglobulinemia develop bacterial type hypersensitivity in response to bacterial products. The evidence presented unfortunately does not provide an unequivocal answer. One of the children (W.A.) developed erythema without induration lasting several days following the intradermal injection of tuberculin. The same reaction was, moreover, observed several times with three different concentrations of old tuberculin. Because of the duration of the erythema it has been tempting to record this as a positive Mantoux reaction and as conclusive evidence that in this patient we have ob-

served dissociation of bacterial type hypersensitivity and classical immune body formation. Induration, however, is an essential part of a truly positive tuberculin reaction. The complete absence of induration, in this instance, prohibits our classifying this reaction as a clear example of bacterial type hypersensitivity. Another observation

was provocative. Minimal erythema and induration occurred following intradermal injection of 1,000 units SK and 250 units SD intradermally in F.H., the 58 year old man. The fact that this reaction occurred only with a very concentrated preparation of SK-SD and not at all with the lower dilutions as well as the fact that it developed only in the

TABLE VI

Delayed (Bacterial-type) Hypersensitivity vs. Streptococcal Products in Children

Vaccine Injected I.D.	Group	Number	Number Positive	Number Negative	%+
Streptokinase 10 u Streptodornase 25 u in 0.1 cc saline	Agammaglobulinemia	5	0	5	0
"	Hospitalized children 7 to 16 years of age	24	23	1	97
"	Hospitalized children 2 to 7 years of age	15	8	7	53
"	Normal adults	16	14	2	88

patient having minimal immunological responsiveness detracts from its significance and makes the observation difficult to interpret.

Contrariwise, as a group, the patients with agammaglobulinemia differ strikingly from the normal population in their reactivity to streptococcal antigens. Seventy-five to 100% of normal children 7 years of age or older show delayed bacterial type hypersensitivity against streptococcal products. In contrast, none of the patients with agammaglobulinemia gave clear evidence of hypersensitivity to the streptococcal antigens used. These observations suggest that patients with agammaglobulinemia have difficulty developing bacterial type hypersensitivity

similar to their handicap in producing circulating antibodies.

Finally, in order for the data on immune reactions to be interpretable it was deemed necessary that the state of complement in the serums of these patients be recorded. Consequently, complement concentrations were determined according to the method of Wedgewood and Janeway on 5 of the patients. For these estimates, blood samples were drawn into sterile tubes, placed in the refrigerator to clot, separated in centrifuge at 4°C and stored at -70°C until used. As will be seen in the Table, the concentration of complement as measured in this way is normal for each of the patients studied.

We must conclude from these observa-

tions that all of the patients with agammaglobulinemia whom we have investigated show a profound immunological handicap. In 4 of the patients no evidence of capacity to form antibody of any kind has been obtained. These 4 patients, we conclude, have a true immunological paralysis. Of the remaining three patients, two young siblings have not been thoroughly studied but appear to be able to form small amounts of antibody against heterologous blood group antigens. A third patient, who has been thoroughly studied, suffers only from severe "immunological paresis."

Hematological Observations in Patients with Agammaglobulinemia - Although Wolfson, et al¹⁰ suggested that agammaglobulinemia may be a disturbance of protein synthesis associated with a failure of lymphocyte production, no thorough hematologic study has been conducted in patients with this disease. The latter authors reported reduced numbers of lymphocytes as a characteristic feature of the circulating blood in one patient with agammaglobulinemia. In contradistinction to Wolfson's observation, none of the 7 cases studied in our laboratory had lymphopenia. Instead, morphologically normal lymphocytes were present in at least normal numbers in both blood and bone marrow of these patients. Several hematological abnormalities were observed, however, which pressed us to investigate thoroughly the hematopoietic tissues in patients with agammaglobulinemia. Further, our longstanding interest in the cellular basis of gamma globulin and antibody production¹⁷ has led us to study the response of the hematopoietic tissues of these patients to antigenic stimulation. Comparison of bone marrow and lymph node changes of normal and agammaglobulinemic subjects following both primary and secondary antigenic stimulation was made. The data obtained from the complete hematological analysis permit the conclusion that patients having agammaglobulinemia show evidence of profound disturbance of the hematopoietic reticulum. We have found, for example, that these patients:

1. regularly exhibit a deficiency of plasma cells in their hematopoietic

centers and in their inflammatory exudates. This deficiency amounts to virtual absence of plasma cells in those having immunological paralysis.

2. regularly fail to respond to even the most intensive antigenic stimulation with either antibody production or plasma cell formation.

3. may respond to bacterial infection with extreme leukocytosis.

4. may develop spontaneously episodes of transient neutropenia, persistent neutropenia, or even may develop apparent cyclic neutropenia.

These latter hematological disturbances cannot, in some instances, be related to either bacterial or virus infections.

In addition to these observations several other hematological disturbances have been found to exist in our patients. In F.H., the adult male having "acquired agammaglobulinemia", the disease developed in apparent association with the occurrence of a large thymoma. The latter tumor was morphologically representative of a benign but intensive local proliferation of the reticulum. In this same patient, study of the bone marrow and peripheral blood revealed virtual absence of eosinophils and their recognizable precursors.

The 26 year old female who also has acquired agammaglobulinemia developed, following the apparent onset of her illness, a profound morphological disturbance of the reticular tissues featured by extensive proliferation of the fixed and free reticulum cells in the spleen, lymph nodes and bone marrow. This reaction was reflected clinically in splenomegaly and lymphadenopathy due primarily to the reticular proliferation. In addition to extensive reticular hyperplasia, however, granulomata (without plasma cells) were observed in the spleen and lymph nodes of the latter patient. In this instance the peripheral blood, except for vigorous neutrophilic response during infection, always either was normal or showed slight lymphocytosis.

As previously mentioned, F.H., a 58

year old male with acquired agammaglobulinemia, possessed almost no eosinophils in either the peripheral blood or bone marrow. This observation prompted a thorough evaluation of the eosinophil content of the blood and bone marrow in the other patients with agammaglobulinemia. The results of this study indicate that eosinophils are developing normally in most of the patients with agammaglobulinemia and show further that eosinophilia may occur in the absence of circulating antibody or gamma globulin if appropriate stimulation is available (. and).

The observation of extreme eosinopenia on hematological analysis of the blood and bone marrow of one of the patients with agammaglobulinemia coupled with knowledge that cortisone and 17 hydroxycorticosterone inhibit antibody production and decrease gamma globulin concentration under certain circumstances prompted investigation of pituitary adrenal function in these patients. Total absolute eosinophil counts performed after the method of Randolph and 17 hydroxycorticosteroid concentration measured by the method of Nelson and Samuels formed the core of this study. The eosinophil and 17 hydroxycorticosteroid concentrations were determined initially and again 2 and 4 hours after stimulation with 25 mg. of ACTH in each of 4 patients with agammaglobulinemia. Normal numbers of eosinophils were present in all except one of the patients studied prior to administration of ACTH. All four patients had normal concentrations of 17 hydroxycorticosteroids in the initial blood sample. Stimulation with ACTH produced a sharp fall in eosinophils and a significant rise in 17 hydroxycorticosteroids in every instance. These data are interpreted as indicating that the pituitary adrenal axis is functioning normally in patients with agammaglobulinemia. They would also seem adequate to eliminate adrenal malfunction as a possible explanation for the syndrome under investigation.

Response of Bone Marrow of Normal Children and Agammaglobulinemic Patients to Antigenic Stimulation - Abnormalities in the cellular distribution within the bone marrow were observed in

each patient. For example, none of these patients showed plasma cells on the routine 500 cell count. In addition, a tendency toward increased numbers of reticulum cells was observed in several instances; further, the forementioned deficiency in development along eosinophil lines was present in one case, F.H., and an arrest in the development of neutrophils in two of the patients, F.T. and T.T., was noted. The plasmacytic deficiency was, however, the only consistent abnormality detected on study of the bone marrow. As for the lymphocytes, their concentration in the marrow in our patients was not decreased in any instance. To the contrary, normal numbers or increased percentages of these elements featured the marrow analysis in all of the patients with agammaglobulinemia.

To gain more incisive evidence on the nature of the hematologic anomaly in patients with agammaglobulinemia, comparison of morphologic changes induced by antigenic stimulation of normal children and agammaglobulinemic patients was carried out. Study of the bone marrows obtained immediately prior to antigenic administration and following three weeks of intensive stimulation with typhoid-paratyphoid vaccine in normal children and patients with agammaglobulinemia were made. Whereas each of 4 normal children developed significant marrow plasmacytosis in response to this stimulation, the 4 patients with agammaglobulinemia did not. No other consistent changes occurred in the marrow as a consequence of the repeated injections of antigen in either group. The failure of the plasmacytic response in patients with agammaglobulinemia is even more striking when large enough numbers of marrow cells are counted so that stable figures for plasma cell percentages are obtained. In each of the agammaglobulinemic patients studied a gross deficiency of this cellular element exists. A sharp rise in the plasma cell content of the bone marrow occurred in each instance along with the development of high antibody titer against the antigen injected. Not so with the agammaglobulinemic patients. None of the latter group developed any evidence of antibody production and none showed evidence of plasma cell prolifera-

tion following stimulation with typhoid and paratyphoid organisms.

Morphological studies indicated that here in human subjects just as in experimental animals antigenic stimulation induces in the bone marrow vigorous maturation of cells of the hematopoietic reticulum along the plasma cell line. In contradistinction, this maturational sequence appears to gain no impetus from antigenic stimulation in the agammaglobulinemic patient.

Comparison of the Response to Antigenic Stimuli of Lymph Nodes from Agammaglobulinemic Patients and Normal Persons - Prior to injection of antigenic substances, lymph nodes were removed by surgical excision from the inguinal region of 5 patients with agammaglobulinemia and from 4 normal persons. Study was made of the lymph node structure and cytology employing fixed tissue preparations stained in the usual way and imprint preparations stained with Romanowski blood stains. Minimal abnormalities of the architecture of the lymph nodes were observed in the lymph nodes of agammaglobulinemic patients. These included:

1. relative thinness of the cortex of the node
2. relative deficiency of primary and secondary follicles
3. relative abundance of fibrous tissues extending out from the hilus of the node.

In the node from one of the agammaglobulinemic patients, L.L., hyperplasia of the fixed reticulum cells and hypertrophy of the node were present as revealed by initial biopsy. Plasma cells were absent from the nodes of each of the agammaglobulinemic patients while an occasional plasma cell was found in the node from each of the normal children prior to antigenic stimulation.

Following preliminary removal of a node, each of the four patients with agammaglobulinemia and each of six normal children were injected intradermally and subcutaneously with 0.5 cc typhoid-paratyphoid immunizing antigen. The

injection was made into the skin and subcutaneous tissue of the thigh. Four days later an inguinal lymph node draining the site of injection was removed surgically from each patient, imprinted, fixed and stained as previously indicated. Hypertrophy of the nodes occurred in each of the 10 subjects. In normal children the changes induced by antigenic stimulation included:

1. increase in size of the lymph nodes
2. increased numbers and activity of germinal centers
3. evidence of increased proliferation of lymphocytes
4. proliferation of the cells of the fixed reticulum
5. cytoplasmic budding of lymphocytes
6. significant plasma cell accumulation, especially pronounced in the medullary cords.

Morphological evidence suggested that in these subjects plasma cells developed largely by heteroplastic metamorphosis from the reticulum of the medullary cords. In contrast, the lymph nodes from patients with agammaglobulinemia who had been given comparable stimulation showed changes comparable to those observed in the normal subjects with the single exception that no plasmacellular proliferation occurred.

Similarly, but even more intensively, the lymph node changes occurring in response to a secondary injection of antigen in normal persons included abundant plasmacellular proliferation in the medullary cords and perifollicular zones. These cells again failed to develop during the secondary response of patients with agammaglobulinemia.

It is concluded from the hematological observations that in each of the seven cases of agammaglobulinemia studied in our laboratory, evidence of profound malfunction of the reticulum was found. The abnormalities noted are summarized in Table VII.

Common to all these cases is a deficiency of development of reticulum cells along plasmacyte lines. This phenomenon is particularly striking when the

TABLE VII

Hematological Disturbances in Patients with Agammaglobulinemia

Patient	Type of hematological disorder observed	Classification of Syndrome
	Transient neutropenia, extreme leukocytosis, absence of plasma cells, failure of plasma cell development on antigenic stimulation.	"Immunological paralysis" congenital
1	Transient neutropenia on several occasions, extreme leukocytosis, absence of plasma cells, failure of plasma development on antigenic stimulation.	"Immunological paralysis" congenital
	Persistent ? neutropenia Absence of plasma cells - failure of plasma cell development on antigenic stimulation	"Immunological paralysis" congenital
	Persistent extreme neutropenia; arrested development of neutrophils in bone marrow, decreased number of plasma cells.	"Immunological paresis" (congenital)
	Cyclic neutropenia, arrested development of neutrophils in bone marrow, decreased number of plasma cells.	"Immunological paresis" (congenital)
	Absence of eosinophils and precursors, thymoma (tumor of fixed reticulum - benign), marked reduction of plasma cells, failure of plasma cell development on antigenic stimulation.	"Acquired immunological paresis"
	Generalized hyperplasia of the fixed reticulum, hemolytic anemia, absence of plasma cells, failure of plasma cell development on antigenic stimulation.	Probably acquired "immunological paralysis"
Young's Case	Lymphopenia	?

response of the reticulum of these patients to antigenic stimulation is compared with that of normal children and adults. In the normal children, proliferation of plasma cells and heteroplastic maturation of the reticulum in the direction of plasma cells is the regular concomitant of antigenic stimulation and consequent antibody production. Such is not the case in agammaglobulinemic patients. In contradistinction, failure of both antibody production and plasma cell accumulation characterize the failure of adjustment of the reticulum of the agammaglobulinemic patients to the demands of antigenic stimulation.

Certain it is that the thymic tumor, the benign but intense reticular hyperplasia, complete lack of eosinophils, transient, persistent and cyclic neutropenias turned up in the hematologic studies of our patients and the lymphopenia observed by Wolfson, et al might each represent diverse actions of bacterial or virus agents on the reticulum. That is to say, it is possible that the hematological disturbances other than the plasmacytopenia may have only an indirect relationship to the agammaglobulinemia. But more attractive to us is the hypothesis that in these diverse but profound hematological disturbances is reflected a disease of the reticulum or

some organizer of reticular function which finds absolute expression in failure of antibody production and plasma cell proliferation.

Response of Patients with Agammaglobulinemia to Gram-Negative Bacterial Endotoxin - The intradermal injection of endotoxins in normal persons results in a skin reaction characterized by erythema, edema, induration, heat and tenderness. Endotoxins administered intravenously produce, with small doses, chills, fever, malaise, and systemic intoxication. Shock and death may result from large doses. Repeated intravenous injections of endotoxin in normal persons results in the development of a high degree of refractoriness to endotoxin.

To investigate the nature of the reactions to endotoxin and to obtain valuable information on the basis for refractoriness against their systemic effects, products containing gram-negative endotoxins were injected into agammaglobulinemic patients. The following observations were made:

1. Agammaglobulinemic patients, just as normals, develop intense local reaction to intradermally injected endotoxins.

2. Chills, fever, malaise and evidence of systemic intoxication occur with equal intensity in agammaglobulinemic and normal persons following the intravenous injection of products containing endotoxin.

3. Refractoriness to the systemic effects of endotoxin occurs with equal facility in normal and agammaglobulinemic subjects.

We may reason from these findings that local reactions to gram-negative endotoxin probably do not involve circulating antibody or capacity to produce antibodies in the usual sense. Systemic reactions to endotoxin are not a function of circulating antibody or the capacity to produce anaphylactic antibody. Refractoriness to the intoxication provided by gram-negative bacterial endotoxin may be completely dis-

sociated from anaphylactic antibody production.

Space does not permit a complete presentation of the data but these revealing experiments of nature have provided us with evidence which dissociates clearly immune body formation and acute phase phenomena. We have, for example, found that the patients with agammaglobulinemia are able to produce C-reactive protein as effectively as are normal subjects, and that they may develop elevations in erythrocyte sedimentation velocity as well as increased serum mucoprotein concentrations. These data suggest, in contradistinction to certain speculation, that C-reactive protein and the several other acute-phase phenomena are dissociated from antibody production.

In addition to these observations, studies have been carried out attempting to initiate immune response in patients with agammaglobulinemia. We have, for example, succeeded in evoking the development of bacterial-type hypersensitivity against streptococcal products in patients with agammaglobulinemia by the intravenous and subcutaneous injection of viable white blood cells from normal persons possessing a high degree of this type of responsiveness. Injection of peripheral white blood cells derived from donors during a period of rapid antibody production against bacterial antigens, however, failed to induce the formation of circulating antibody.

Successful Homotransplantation of Skin in a Patient with Agammaglobulinemia - One of the great obstacles to medical progress in our era is the fact that homotransplantation is regularly unsuccessful. Although it has been suspected that the homotransplantation failure has an immunological basis, proof of this hypothesis is lacking. As well conceived and properly controlled studies have replaced haphazard clinical observation it has become apparent that in man and other mammals, orthotopic homotransplants always result in the eventual destruction and ultimate biologic replacement of the transplanted tissue. Homotransplantation of skin has been successful only between monozygotic twins in man or among individ-

ual members of highly inbred strains of experimental animals. Medawar, et al²¹ along with others²²⁻²⁵ have provided substantial evidence for the immunologic theory of transplantation failure in experimental animals. This evidence includes data that in experimental animals:

1. the time required for rejection of homotransplants is approximately the same as that required for antibody formation.

2. the rate of transplantation rejection is a function of the dose of "antigen" supplied.

3. circulation (blood or lymph) without a barrier to antibody is essential for the rejection of homotransplants.

4. evidence for an anamnestic reaction toward homotransplants has been obtained.

5. agents decreasing antibody formation prolong the survival of homotransplants.

6. rejection of skin transplants is accompanied by the appearance in the blood of antibody against donor cells.

In the course of study of our patients with agammaglobulinemia and immunological paralysis it was decided that homografting of skin should be attempted primarily for two reasons, namely:

1. to gain evidence on the basis for homotransplantation failure in man.

2. as an initial step in possible replacement therapy in these patients if the deficient system could be identified.

Consequently, the following experiment was performed: Skin taken from an agammaglobulinemic child was placed on a clean granulating surface of another unrelated child of different blood type. The recipient was a child capable of accepting autotransplants with facility. At the same time skin taken from a 45 year old lady of blood

group A was placed on the denuded area of the 7 year old boy with agammaglobulinemia, blood group O. In the former instance the tattooed full thickness graft showed a splendid initial take and was then rejected with complete necrosis and slough occurring within a period of one month. This is the usual fate of skin homotransplants. To the contrary, the split thickness and full thickness skin homograft placed on the patient with agammaglobulinemia have taken, grown, and are still surviving without showing any reaction 7 months after application.

Discussion

Many points presented by the observations made in the course of this investigation require discussion and elaboration. Because of the limitations in space, most of these will be left to future reports and the definitive publication of the individual observations. It has been the purpose of this report to call to your attention the clinical syndrome presented by patients with agammaglobulinemia, to report studies designed to elucidate the underlying mechanisms of this metabolic disorder, and to emphasize the phenomenal opportunity provided by the availability of these patients, as experiments of nature, to delve into unsolved problems in immunology.

The discovery of 7 such cases in the 9 month period that this study has been in progress, we feel to be a true reflection of the relative frequency of this syndrome. These patients undoubtedly have not been discovered clinically in the past because the disease, as we now know it, did not exist. It seems unlikely that patients with such an extreme susceptibility to bacterial infection would have survived even the first year of life in the pre-antibiotic era. Just one of the attacks of meningitis or pneumonia would have been sufficient to destroy almost all of them. They represent, then, a true product of the antibiotic era not in the sense that antibiotics are responsible for the metabolic disorder itself but because the sulfa drugs and antibiotics have permitted sufficiently long survival so that

the clinical disease becomes apparent. From the observations made up to the present time it seems likely that a substantial proportion of patients who suffer from recurrent bacterial infection are in trouble because of an immunological handicap such as that underlying the agammaglobulinemia in our patients.

The concept that agammaglobulinemia may be subdivided into congenital and acquired forms receives vigorous support from our observations. The fact that the 5 children studied in our laboratory are all boys representing three families supports the proposal that the congenital form of agammaglobulinemia represents an inborn error of metabolism transmitted as a sex-linked recessive trait. The two adult patients of our series, being a 58 year old male having clinical disease of 4 years duration and a 26 year old female who has been ill for 8 years, support the concept that agammaglobulinemia may be acquired in either sex at any age.

Our discovery that patients with agammaglobulinemia regularly show evidence of disease of the reticulum provides valuable information. In the first place it dictates the necessity of looking for this underlying disturbance of immune mechanism in patients with granulocytopenia, agranulocytosis and even cyclic neutropenia. Secondly it provides us with a reasonably likely target cell in our quest for knowledge of the cellular mechanisms of antibody and gamma globulin elaboration. From these observations the fixed and free reticulum and ultimately their plasma cell derivatives assume predominance in our struggle to erect hypotheses which will lead to better understanding of the immune mechanism and its ultimate control.

More than provocative are the individual observations on the reactivity of these patients to the variety of stimuli provided. Obviously from these results, much needs be learned concerning the basis of resistance to and recovery from virus infections, the relationship of anaphylactic antibody production to bacterial type hypersensitiv-

ity, the true nature and mechanisms involved in development of bacterial type-hypersensitivity, the basis for local and systemic reactions to gram-negative bacterial endotoxins, the nature of refractoriness against the systemic action of endotoxins and the significance of basis for acute phase reactions. Although observations made in the agammaglobulinemic patients have not solved these biological problems they have narrowed the possible avenues of approach considerably in each instance.

Perhaps the most provocative of these many observations is the one made by Dr. Varco and myself concerning the feasibility of homotransplantation in the absence of immunological reactivity. The observation too that agammaglobulinemia may be an acquired disease is particularly stimulating in this regard.

These two observations taken together provoke us to speculate that ultimate universal homotransplantation with its obvious advantages to all of medicine might gain reality through relatively simple immunological manipulations rather than through some fantastically complicated system of tissue and organ matching. Observations on the agammaglobulinemic patients suggest possible approaches to this problem. Speculating further in this same vein it seems likely that many of the unsolved problems of medicine might yield to methods providing even temporary control of the immune response. A few of these unsolved problems which pop quickly to mind include the wastage of pregnancy due to erythroblastosis fetalis, the annoyance of allergy, the now numerous life threatening autoimmune hematologic disorders which clearly represent a misdirected immune response, and polyarteritis nodosa, lupus erythematosus, rheumatic fever, nephrosis and nephritis, any or all of which might be based on mistaken or misdirected host reaction. Intensive investigation of the provocative experiment of nature represented by the agammaglobulinemic patients could well be the incisive approach needed to permit accumulation of knowledge which would provide control of the mechanism of adjustment, disturbed in these patients, which can operate deleteriously

as well as beneficially for the host.

From the practical standpoint the patients themselves present a problem demanding attention. Doubtless we can help them greatly by giving intramuscular injections of gamma globulin synthesized by intact humans and by providing prophylactic antibiotic therapy against many infections. But doing this we leave them with the residual handicap of immunological unresponsiveness. A driving force in our laboratory is a desire to induce in these patients a capacity to react to antigenic material. A glimmer of light in this direction perhaps is the observation that skin reactivity to streptococcal products can be induced in these patients by the parenteral administration of viable white blood cells. Further experiments along this line are both in progress and being contemplated. It is our conviction that should we discover a means of inducing antibody production in the patient with agammaglobulinemia, our studies will not only have been of real service to him but we also will have taken a big step toward ultimate control of immunological phenomena.

Summary

1. Seven patients having agammaglobulinemia are described. These include 5 male children having the congenital disease and 2 adults with the acquired form.

2. The basic clinical problem presented by the extreme susceptibility of these patients to bacterial infection is considered.

3. Simple methods for diagnostic screening are suggested. These include measurement of the zinc turbidity reaction of the serum and titration of isohemagglutinins against heterologous blood group cells.

4. The existence of a profound immunological handicap in each of these patients is reported. Four were shown to have "immunological paralysis" while three showed evidence of minimal immuno-

logical reactivity.

5. Profound hematological disturbances in each of the agammaglobulinemic patients are described. These include various forms of neutropenia, eosinopenia, thymic tumor and generalized proliferation of reticulum cells.

6. A deficiency of plasma cells in the hematopoietic tissues and failure of plasma cellular development from reticulum in response to antigenic stimuli is reported.

7. That all of the hematological abnormalities occurring in patients with agammaglobulinemia have their common denominator in failure of heteroplastic maturation of the reticulum is suggested.

8. Identical reactions of agammaglobulinemic patients and normal persons to parenteral injections of gram-negative bacterial endotoxins are reported.

9. Similarity of acute-phase serological reactions in agammaglobulinemic and normal subjects is mentioned.

10. Transmission of bacterial type hypersensitivity against streptococcal products by injection of white blood cells from streptococcal sensitive donors is reported.

11. Successful homotransplantation of skin in a patient with agammaglobulinemia is described.

12. The possible implications of these observations on immunological theory and future approach to immunological problems is discussed.

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II. MEDICAL SCHOOL NEWS

Coming Events

- October 11 - 13 Continuation Course in Tuberculosis Control for Lay Persons
October 14 - 16 Continuation Course in The Use of the Minnesota Multiphasic Personality Inventory (MMPI) for Clinical Psychologists
October 21 and 22 Dedication of the Mayo Memorial
October 21 Minnesota Medical Foundation Luncheon; Junior Ballroom, Coffman Memorial Union; 12:00 noon.
October 21 Dedication Banquet; Main Ballroom, Coffman Memorial Union; 6:30 p.m.
October 22 Meeting of the Minnesota Medical Alumni Association; Mayo Memorial Auditorium; 1:30 p.m.
October 22 Homecoming Clinics; Eustis Amphitheater; 2:00-4:00 p.m.
October 22 Minnesota Medical Alumni Association Banquet and Dance; Radisson Hotel; 6:30 p.m.
November 4-6 Continuation Course in Anesthesiology for General Physicians

* * *

Greetings

For those of us associated with the Medical School, Fall is always a pleasant, stimulating, and busy time. The resumption of classes and the season itself combine to produce an invigorating effect unmatched during the rest of the year.

This Fall is even more significant than usual. Many of us have already moved into new quarters in the Mayo Memorial and others will do so shortly. In his Greetings, which appear on another page of this issue, Dean Diehl has stated concisely and well what the new facilities mean to all of us. The Dedication of the Mayo Memorial on October 21 and 22 represents the culmination of more than a decade's efforts on the part of many people.

It is, indeed, a particular pleasure this year to extend greetings to students, faculty, members of the Minnesota Medical Foundation, and to all friends of the Medical School. We hope that all of you who are not yet familiar with the Mayo Memorial will take the opportunity of seeing it on October 21 and 22.

* * *

Mayo Memorial Dedication

By this time all of the regular readers of the Bulletin should have received announcements of the Mayo Memorial Dedication Exercises which will be held on October 21 and 22. They will have noted that the two-day program includes guided tours of the new building, a series of lectures by outstanding authorities in the medical sciences, and a Dedication Banquet which will take place on Thursday evening, October 21, at 6:30 p.m. in the Main Ballroom of Coffman Memorial Union.

We would like to urge all of our readers to attend as much of the dedication program as their busy schedules will permit. With the support of the Minnesota Medical Foundation, a limited number of tickets for the banquet has been made available at a reduced rate to medical students, interns, fellows, and teaching assistants.

Further information concerning any aspect of the Dedication Exercises may be obtained from the Chairman, Committee on the Dedication of the Mayo Memorial, Room 1342 Mayo Memorial.

Minnesota Medical Foundation

Members of the Minnesota Medical Foundation will take particular pride in the Dedication of the Mayo Memorial, since so many of them were generous contributors to the Memorial Fund. Customarily the first Thursday of the school year is Minnesota Medical Foundation Day. This year, however, Foundation Day events will take place at the time of the Mayo Memorial Dedication.

A luncheon meeting has been arranged for 12:00 o'clock noon on Thursday, October 21, in the Junior Ballroom of Coffman Memorial Union. Dr. Owen H. Wangenstein, President, will present a brief summary of the year's activities. Dr. Robert B. Howard will report on the membership and also on the "Bulletin of the University of Minnesota Hospitals and Minnesota Medical Foundation." Those undergraduate students selected as recipients of scholarships during the year 1954-55 will also be present at the luncheon. The report of the Nominating Committee for new members of the Board of Directors will be made.

The meeting will be interesting and brief. Immediately following the luncheon, guests will join the gathering in the Mayo Memorial Auditorium where the dedication exercises will reconvene at 1:30 p.m.; and at this time, the scholarships will be awarded to the students.

* * *

Minnesota Medical Alumni Association

The Minnesota Medical Alumni Association is also participating actively in the Mayo Memorial Dedication Exercises. Homecoming for Medical Alumni will be held at the time of the Dedication, October 21 and 22. Officers of the Medical Alumni Association hope that a large number of alumni will turn out for the two-day dedication program and for the Homecoming events which will be of special interest to Minnesota graduates.

The Annual Meeting of the Minnesota Medical Alumni Association will take place at 1:30 p.m. on Friday, October 22, in the new Mayo Memorial Auditorium, immediately following the Hospital Staff Meeting. From 2:00 to 4:00 p.m. Homecoming Clinics will be given in Eustis Amphitheater. At 6:30 p.m. that evening a Medical Alumni Association Banquet will be held at the Radisson Hotel. A dance will follow the banquet.

* * *

Dr. Tobian Joins Faculty

We are pleased to welcome to our faculty as Associate Professor of Medicine Dr. Louis Tobian. Dr. Tobian, a 1943 graduate of Harvard Medical School, comes to us from Southwestern Medical School in Dallas, Texas. He is an Established Investigator of the American Heart Association and will continue his fundamental investigations on hypertension and arteriosclerosis. His presence here will give added impetus to our cardiovascular research program.

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(Continued on next page)

Promotions

Congratulations are in order to the following members of our faculty who have received academic promotions:

Promoted to Professor

Annie Laurie Baker	Department of Social Service
Frederic E. B. Foley	Division of Urology

Promoted to Associate Professor

William C. Bernstein	Division of Proctology
Jacob Blumenthal	Department of Medicine
Paul S. Hagen	Department of Medicine
Harry B. Hall	Division of Orthopedic Surgery
Henry V. Hanson	Division of Otolaryngology
William Stead	Department of Medicine
Frederick H. Van Bergen	Division of Anesthesiology
Leslie Zieve	Department of Medicine

Promoted to Assistant Professor

Paul Adams	Department of Pediatrics
Donald S. Amatuzio	Department of Medicine
Charles W. Carr	Department of Physiological Chemistry
Jack Friedman	Department of Radiology
Benjamin Fuller	Department of Medicine
Beulah T. Gautefald	School of Nursing
Albert J. Greenberg	Department of Medicine
Irwin H. Kaiser	Department of Obstetrics and Gynecology
Paul H. Lober	Department of Pathology
Agnes D. Love	School of Nursing
Elizabeth Lowry	Department of Pediatrics
Frank Martin	Department of Medicine
Malvin J. Nydahl	Division of Orthopedic Surgery
Verna Rausch	Medical Technology
Hildred M. Schuell	Department of Psychiatry and Neurology
Alvin Schultz	Department of Medicine
Ralph E. Smith	Department of Medicine

Promoted to Instructor

Rolf L. Andreassen	Department of Medicine
David L. Fingerman	Department of Medicine
John J. Galligan	Department of Pediatrics
Helen Hislop	Department of Physical Medicine and Rehabilitation
William Krivit	Department of Pediatrics
Walter F. Larrabee	Department of Medicine
George W. Lund	Department of Pediatrics
Marguerite Schwyzer	Department of Medicine

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III.

UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
WEEKLY CALENDAR OF EVENTS

Physicians Welcome

October 11 - 16, 1954

Monday, October 11

Medical School and University Hospitals

- 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; W-612, U. H.
- 10:00 - 12:00 Neurology Rounds; A. B. Baker and Staff; Station 50, U. H.
- 11:30 - Tumor Conference; Doctors Hitchcock, Zimmermann, and Stenstrom; Todd Amphitheater, U. H.
- 12:15 - Obstetrics and Gynecology Journal Club; Staff Dining Room, U. H.
- 12:30 - 1:30 Physiology Seminar; Kinetics of Sodium Exchange in Frog Heart and Muscle; John A. Johnson; 214 Millard Hall.
- 1:30 - 2:30 Pediatric-Neurological Rounds; R. Jensen, A. B. Baker and Staff; U. H.
- 1:30 - 3:30 Dermatology Hospital Rounds; H. E. Michelson and Staff; Dermatology-Histopathology Room, M-434, U. H.
- 4:30 - Pediatric-Medicine Infectious Disease Rounds; Station 33, U. H.
- 5:00 - 6:00 Physiology-Surgery Conference; Todd Amphitheater, U. H.
- 5:00 - 6:00 Urology-Roentgenology Conference; C. D. Creevy, O. J. Baggenstoss and Staff; Eustis Amphitheater.

Ancker Hospital

- 8:30 - 10:30 Medical and Surgical Chest Conference; Dr. Gehlen and Staff; Auditorium.
- 10:00 - 12:00 Surgery Grand Ward Rounds; Begin Floor E4.
- 11:00 - 12:00 Medicine Resident Rounds.
- 12:30 - 2:30 Surgery Out-Patient Clinic; Room 8.
- 2:00 - 3:00 Routine EKG Interpretation; Dr. Sommers and House Staff; Medical Record Library.
- 2:30 - 3:00 Discussion of Problem Case; Auditorium.
- 3:00 - 4:00 Surgery Journal Club; Classroom.
- 3:00 - 4:00 Lectures on Electrocardiography; Ben Sommers; Auditorium.

Minneapolis General Hospital

- 9:30 - Pediatric Rounds; Richard Raile; Station K.
- 10:30 - 12:00 Medicine Rounds; Thomas Lowry; Station F.
- 11:00 - Orthopedic and Fracture Rounds; Drs. John Moe and Arthur Zierold; Station B.

Monday, October 11 (Cont.)

Minneapolis General Hospital (Cont.)

- 11:00 - Pediatric Seminar; Erling Platou; Classroom, Station M.
- 12:30 - Surgery Grand Rounds; Dr. Zierold; Station E.
- 1:30 - 2:30 Tuberculosis Conference; J. A. Myers; Station M.
- 2:00 - Pediatric Rounds; Stations I and J.

Veterans Administration Hospital

- 9:30 - Infectious Disease Rounds; Drs. Hall, Zinnemann, and Middlebrook.
- 1:30 - Cardiac Conference; Drs. Smith, Berman, Hoseth, Simonson, Swerdlow, Shapiro, and J. Brown; Conference Room, Bldg. I.; Rounds immediately following conference.

Tuesday, October 12 (HOLIDAY)

Wednesday, October 13

Medical School and University Hospitals

- 8:00 - 9:00 Roentgenology-Surgical-Pathological Conference; Paul Lober and L. G. Rigler; Todd Amphitheater, U.H.
- 11:00 - 12:00 Pathology-Medicine-Surgery-Pediatrics Conference; Todd Amphitheater, U. H.
- 1:00 - 2:00 Dermatology Clinical Seminar; F. W. Lynch; 300 North Clinic.
- 1:30 - 3:00 Pediatric Allergy Clinic; Albert V. Stoesser and Lloyd Nelson; W-211, U. H.
- 3:30 - 4:30 Dermatology-Pharmacology Seminar; 3rd Floor Conference Room, Heart Hospital.
- 4:30 - 5:50 Dermatology-Infectious Disease Seminar; 3rd Floor, Conference Room, Heart Hospital.
- 5:00 - 5:50 Urology-Pathological Conference; C. D. Creevy and Staff; Eustis Amphitheater, U. H.
- 5:00 - 6:00 Residents' Lecture; Cardiac Catheterization; Paul Adams; Conference Room, X-ray Department, U. H.
- 5:30 - 7:30 Dermatology Journal Club and Discussion Group; Hospital Dining Room.
- 7:30 - 9:30 Dermatology Seminar; Review of Interesting Slides of the Week; Robert W. Goltz; Todd Amphitheater, U. H.
- 7:30 - Physiology 114A Seminar; Hemodynamic Problems; M. B. Visscher and Robert Evans; 271 Lyon Laboratories.

Ancker Hospital

- 8:30 - 9:30 Clinico-Pathological Conference; J. Noble; Auditorium.
- 11:00 - 12:00 Medicine Resident Rounds.

Wednesday, October 13 (Cont.)

Minneapolis General Hospital

- 8:30 - 9:30 Obstetrical and Gynecological Grand Rounds; William P. Sadler and Staff; Station C.
9:30 - Pediatric Rounds; Henry Staub; Station I.
10:30 - 12:00 Medicine Rounds; Thomas Lowry and Staff; Station D.
1:30 - Pediatric House Staff Seminar; Erling Platou; Station I.
1:30 - Pediatric Rounds; Erling Platou; Classroom, Station I.

Veterans Administration Hospital

- 8:30 - 10:00 Orthopedic X-ray Conference; E. T. Evans and Staff; Surgical Conference Room, Bldg. 43.
8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker.
9:00 - Gastro-Intestinal Rounds; Drs. Wilson, Zieve, Ferguson, Brakel, O'Leary, Konig, and Swenson.
11:00 - Gastroenterology Conference; Conference Room, Bldg. I.
12:30 - Medical Journal Club; Doctors' Dining Room.
12:30 - X-ray Conference; J. Jorgens; Conference Room, Bldg. I.
1:30 - 3:00 Metabolic Disease Conference; Drs. Flink and Latts.
3:30 - Urology Pathology Slide Conference; Dr. Gleason; Conference Room, Bldg. I.
7:00 - Lectures in Basic Science of Orthopedics; Conference Room, Bldg. I.

Thursday, October 14

Medical School and University Hospitals

- 9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; Room 3.148; Mayo Memorial.
11:00 - 12:00 Cancer Clinic; K. Stenstrom, A. Kremen, and B. Zimmermann; Todd Amphitheater, U. H.
12:30 - Anatomy Seminar; Correlated Anatomical and Physiological Studies of the Hippocampus; Berry Campbell; 226 Jackson Hall.
12:30 - Physiological Chemistry Seminar; Transamination; Kenneth Woods; 214 Millard Hall.
1:30 - 4:00 Cardiology X-ray Conference; Heart Hospital Theatre.
5:00 - 6:00 Radiology Seminar; Absence of Intestinal Gas in Infants; Drs. Conklin and Margulis; Eustis Amphitheater, U. H.

Thursday, October 14 (Cont.)

Ancker Hospital

- 8:30 - 9:30 Medical Grand Rounds; Auditorium; Visiting Staff Rounds immediately following Grand Rounds.
- 11:00 - 12:00 Medicine Resident Rounds.
- 2:00 - 3:00 Routine ECG Interpretation; Ben Sommers; Medical Record Library.

Minneapolis General Hospital

- 9:30 - Neurology Rounds; Heinz Bruhl; Station I.
- 9:30 - Pediatric Contagion Rounds; R. B. Raile; Station K.
- 10:00 - Psychiatry Grand Rounds; R. W. Anderson and Staff; Station H.
- 11:30 - 12:30 Clinical Pathological Conference; John I. Coe; Classroom.
- 12:30 - 2:30 Dermatology Rounds and Clinic; Carl W. Laymon and Staff.
- 1:00 - Fracture X-ray Conference; Drs. Zierold and Moe; Classroom.
- 1:00 - House Staff Conference; Station I.

Veterans Administration Hospital

- 8:30 - Hematology Rounds; Drs. Hagen and Williams.
- 8:30 - Experimental Surgery Laboratory Meeting; Conference Room, Bldg. I.
- 9:00 - Surgery Grand Rounds; Conference Room, Bldg. I.
- 9:00 - Surgery Ward Rounds; D. Ferguson and Staff; Ward 11.
- 11:00 - Surgery-Roentgen Conference; J. Jorgens; Conference Room, Bldg. I.

Friday, October 15

Medical School and University Hospitals

- 8:00 - 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.
- 10:30 - 11:50 Medicine Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.
- 10:30 - 1:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.
- 11:00 - 12:00 Vascular Rounds; Davitt Felder and Staff Members from the Departments of Medicine, Surgery, Physical Medicine, and Dermatology; Eustis Amphitheater, U. H.
- 11:45 - 12:50 University of Minnesota Hospitals Medical Staff Meeting; Subject and Speaker to be announced; Mayo Memorial Auditorium.
- 1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.

Friday, October 15 (Cont.)

Medical School and University Hospitals (Cont.)

- 1:30 - 2:30 Dermatology Grand Rounds; Presentation of Cases from Grouped Hospitals (University, Ancker, General and Veterans) and Private Offices; H. E. Michelson and Staff; Eustis Amphitheater, U. H.
- 2:30 - 4:00 Dermatology Hospital Rounds; H. E. Michelson and Staff; Begin at Dermatological Histopathology Room, M-434, U. H.
- 3:00 - 4:00 Neuropathological Conference; F. Tichy; Todd Amphitheater, U. H.
- 3:30 - 4:30 Dermatology-Physiology Seminar; 3rd Floor Conference Room, Heart Hospital.
- 4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hanson and Staff; E-534, U. H.
- 5:00 - Urology Seminar and X-ray Conference; Eustis Amphitheater, U. H.

Ancker Hospital

- 3:00 - 4:00 Medical-Surgical-Pathological Conference; Auditorium.
- 4:00 - 5:00 Medical Journal Club; Conference Room, E5.
- 4:00 - 5:00 X-ray Surgery Conference; Auditorium.

Minneapolis General Hospital

- 9:30 - Pediatric Rounds; Elizabeth Lowry; Station J.
- 10:30 - Pediatric Surgical Conference; Tague Chisholm and B. Spencer; Classroom, Station I.
- 12:00 - Surgery-Pathology Conference; Drs. Zierold and Coe; Classroom.
- 1:00 - 3:00 Clinical-Medical Conference; Thomas Lowry; Classroom, Station M.
- 1:30 - Pediatric Contagion Rounds; L. Wannamaker; Station K.

Veterans Administration Hospital

- 10:30 - 11:20 Medicine Grand Rounds; Conference Room, Bldg. I.
- 12:30 - Urology X-ray Conference; X-ray Department.
- 1:00 - Autopsy Conference; E. T. Bell; Conference Room, Bldg. I.
- 2:00 - Pathology Slide Conference; E. T. Bell; Conference Room, Bldg. I.

Saturday, October 16

Medical School and University Hospitals

- 7:45 - 8:50 Orthopedic X-ray Conference; W. H. Cole and Staff; M-109, U. H.
9:00 - 10:30 Pediatric Grand Rounds; Eustis Amphitheater, U. H.
9:00 - 11:00 Anesthesiology Seminar; F. H. Van Bergen and Staff; 5162 Mayo Memorial.
9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; Heart Hospital Amphitheater.
9:15 - 10:00 Surgery-Roentgenology Conference; L. G. Rigler, J. Friedman, Owen H. Wangenstein and Staff; Todd Amphitheater, U. H.
10:00 - 11:30 Surgery Conference; Todd Amphitheater, U. H.
10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

Ancker Hospital

- 8:30 - 9:30 Surgery Conference; Auditorium.
9:30 - 11:00 Medicine Grand Ward Rounds.

Minneapolis General Hospital

- 8:00 - Urology Staff Conference; T. H. Sweetser; Main Classroom.
9:00 - Psychiatry Grand Rounds; R. W. Anderson; Station H.
9:30 - Pediatric Rounds on all Stations; R. B. Raile.
11:00 - 12:00 Medical X-ray Conference; O. Lipschultz, Thomas Lowry and Staff; Main Classroom.

Veterans Administration Hospital

- 8:00 - Proctology Rounds; W. C. Bernstein and Staff; Bldg. III.
8:30 - Medical X-ray Conference; Conference Room, Bldg. I.