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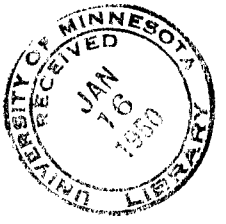

Experimental Cardiovascular Disease, Rheumatic Type

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I. EXPERIMENTAL STUDIES IN CARDIOVASCULAR DISEASE, RHEUMATIC TYPE*,**

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The importance of rheumatic fever as the leading cause of death between the ages of 5 and 10 years and as the cause of approximately 35 per cent of all heart disease is well known. Obvicusly, it presents a vital subject for research.

Information resulting from clinical investigation and basic research has accumulated over many years to make available countless pieces which must be integrated in any attempt to solve the puzzle of the clinical syndrome recognized as rheumatic fever. Especially helpful for perspective is to compare the problem to the critical wounding of the heart by gun-fire. Of the three stages in such a sequence, the first stage is the trigger mechanism and detonation which, for rheumatic fever, reflects the initiation of illness; the second, the explosive phase or the development of rheumatic disease; and the third, the mark or target, is analogous to the host and its response, inclusive of the residual or permanent damage. This simple analogy provides an opportunity to focus attention upon the objectives and the limited accomplishments which have come from three years of experimental work in our laboratory.

The three phases that commonly occur clinically in rheumatic fever were emphasized by Escherich and Schick[1]. The initial streptococcal infection sets off the trigger mechanism. The latent phase, Phase II, which is asymptomatic and inapparent, is followed by the explosive phase, Phase III, with the development of active clinical disease. The reaction of the host and the residual damage represent the target. This analogy to a trigger has been applied by others[2,3]. Phase II, the latent phase, suggests that sensitization to a streptococcal component may have occurred.

The Factor of Hypersensitivity

Soon after it was recognized that serum disease and serum shock in man and anaphylactic shock in animals resulted as the response of the host to secondary contact with the same antigen, usually a foreign protein, the possibility that the variegated manifestations of rheumatic fever might result from an antigen - antibody reaction has been under consideration. The suggestion apparently first was made in 1902 by Menzer[4] at a time when the concept of allergy was new. Haig-Brown in 1899[5], von Pirquet and Schick[6], and Escherich and Schick[1] in 1912 were especially impressed with the latent period that occurs between the streptococcal infection and the appearance of rheumatic symptoms. In succeeding years, many investigators have been led to conclude from their experimental results that the allergic tissue reactions are essentially similar to what may result in the rheumatic state. While these studies are not sufficiently conclusive to be generally accepted, they are highly suggestive. The employment of large doses of foreign protein has resulted in tissue changes suggestive in some instances of periarteritis nodosa and in others of rheumatic fever[7-11]. It, therefore, seems not inconceivable that the basic mechanism of allergy plays a dominant role in the pathogenesis of rheumatic fever.

The Streptococcal Factor

The antigenic components of the streptococci determine the serologic classifications of Lancefield[12] and of Griffith[13]. The Lancefield classification, which is based on the immunologic measurement of chemically separable components, has come to be generally accepted as a laboratory procedure for the identification of hemolytic streptococci. These cocci are separable by differences in a carbohydrate component, the "C" sub-

*This research was conducted under contract with the Office of Naval Research.

stance, into twelve groups which are designated A to N, exclusive of I and J. Further serological subdivision has been accomplished for some of the groups. Group A has been demonstrated in approximately 95 per cent of streptococcal infections in man[14]. For group A, the type specific substance is a proteinaceous constituent, the "M" substance. Immunologically separable "M" substances make possible the separation of group A hemolytic streptococci into 40 types, or more.

The microbiologic products are numerous. These include streptolysin-O, streptolysin-S, streptokinase, erythrogenic toxin, hyaluronic acid, hyaluronidase, desoxyribonuclease (DORNase), ribonuclease, and proteinase.

The role in the pathogenesis of rheumatic fever is not known for a single streptococcal component or product. Such information as exists is derived from the indirect evidence of antibody production in human infections[15-19]. The factors that determine the activity of the streptococci are ill defined; and the conditions under which the products are active, e.g., streptolysin-S is formed largely in the presence of ribonucleic acid (cells of host), indicate somewhat obscure interrelationships. The result is that reflections of reactivity are visualized by assays of antibodies or of inhibitors in the blood.

It is of interest to point out the diversity of interreactions which occur between streptococcus and its substrate. These reactions may occur only in vivo or in vitro or under both conditions. As an example, streptolysin-O is altered from its natural precursor, a substance containing -S-S- linkage, to the -SH or sulfhydryl group which causes the toxin to become hemolytically active[20].

Difficulties may be encountered in interpretation of the role of precursors[21]. Thus, Crowley[22] found the production of hyaluronidase limited to types 4 and 22, whereas it was shown by Pike[22a] that hyaluronidase was produced by more than half of the strains of group A streptococci which were studied in his laboratory. This latter finding may represent an example[23] of an adaptive enzyme system. Evidence to support the ability of streptococci to form hyaluronidase in vivo is the production of specific antibodies, antihyaluronidase, brought about during most group A streptococcal infections[21].

As a second example, streptokinase (streptococcal fibrinolysin) is elaborated by streptococci of group A, as well as by some of groups C and G, and rarely by members of group B. This enzyme[24] participates in a catalytic role as an activator of the proenzyme, plasminogen, which is present in all human sera[25]. In the dynamics of this mechanism, a second naturally occurring substance in blood, antiprotease, serves as an effective inhibitor, but it is not an antibody.

Before consideration of our own experimental work, perhaps the best example of this sequence of changes brought about through animal experimentation is the recent work reported by Murphy and Swift[26]. This contribution to an understanding of rheumatic fever represents the culmination by Dr. Swift of thirty years of concentrated study in this field. Murphy and Swift infected rabbits by successive focal cutaneous inoculations of different immunological types of group A streptococci over a period of as long as two and a half years. Some of their animals became sick although many recovered. Among the animals killed two weeks after the final injections, most of them gave no evidence of streptococcal bacteremia at autopsy, while a few yielded positive blood cultures. Lesions observed in these animals were in heart valves as well as in the myocardium and were interpreted as closely resembling the lesions encountered in the hearts of patients dying of rheumatic fever. It was emphasized that the lesions in these animals were not those of panarteritis of the allergic or periarteritic type. Of especial interest, as it may reflect the role of the endocrine system,

was the observation that the rabbits with cardiac lesions had markedly enlarged adrenal glands.

EXPERIMENTAL

The premises for our experimental studies were several. In the first place, the evidence in support of an intimate relationship of streptococci to rheumatic fever has been epidemiological[27,28] and circumstantial. The circumstantial evidence suggests that an allergic component may be responsible for the systemic manifestations and the hyperergic tissue reactions of this disease process. There are two hypotheses which may be advanced in the attempt to explain the sequence of events. In the first, it can be assumed that the primary infections through the release of streptococcal products bring about the sensitization of the tissues. In subsequent infections, streptococci release the same sensitizing substances to bring about an antibody reaction in fixed tissues which is reflected clinically as episodes of acute rheumatic fever. An alternative, but basically similar tenet, is that a streptococcal product or constituent injures tissue cells to release an antigenic substance which in turn elicits an autoantibody[29-31]. Such an autoantibody might conceivably be limited in its reactivity to the homologous host cell, or to a complex antigen combination made up of host cell and some streptococcal derivative functioning in a haptenic role. It would follow that any subsequent streptococcal infection through release of a streptococcal hapten might react with fixed tissue antibody to elicit a tissue response and clinical symptoms.

In an attempt to learn the reactivity of the cardiovascular system to the constituents of the streptococcus, normal animals and animals with an altered tissue reactivity brought about by hypersensitization were injected repeatedly with hemolytic streptococci of group A which had been inactivated *in vitro* by penicillin. The results presented herewith are limited to the findings of experiments in which rabbits and monkeys were employed as the host animal.

Two host species were employed in two series of experiments to determine whether an altered tissue reactivity brought about by hypersensitization to a foreign protein, either horse serum or crystalline egg albumin, would condition the reactivity of the cardiovascular system to streptococcal constituents to result in a rheumatic-like disease. The effects were measured in from two to eleven months after the initial exposure to antigen by the histopathological study of the heart, the large vessels, and representative sections from other organs and tissues of the host.

Series A. Rabbits

Experiment 1. - Horse serum was employed as a foreign protein for the sensitization of the tissues of 23 rabbits by the injection intravenously of 10 ml. per kilogram body weight in from 1 to 13 doses at intervals of from 1 to 20 weeks. Five of these animals, as controls, were given horse serum; six, as controls, received horse serum and penicillin or sulfadiazine; six received horse serum, penicillin or sulfadiazine and streptococcal supernatant fluid; six were given horse serum and streptococci which had been inactivated by penicillin or sulfadiazine.

The findings of Experiment 1 are summarized in Table I. Histopathological evidence of an inflammatory reaction was present in 19 of the 23 rabbits. Myocarditis was the most common finding; involvement of the valvular and mural endocardium was next in frequency. Pericarditis, arteritis, and periarteritis occurred in about a fourth of the rabbits. Horse serum alone, or in combination with streptococcal constituents, produced the highest incidence and the most extensive changes. The changes in most of the animals were readily recognizable but minimal, a 1+ reaction. The two animals that revealed in sections of myocardium Aschoff-like nodules were from the groups that had received

Table I

EXPERIMENTAL CARDIOVASCULAR DISEASE IN RABBITS

	ENDOCARDITIS		MYO-CARDITIS	PERI-CARDITIS	ARTERITIS	PERI-ARTERITIS
	Valvular	Mural				
1. Foreign Protein	7/7	4/7	7/7	5/7	5/7	4/7
2. Foreign Protein + Pen. or S.A.D.	6/8	4/8	5/8	2/8	1/8	2/8
3. Strep. Supernat. + (2)	1/6	1/6	3/6	1/6	0/6	0/6
4. Foreign Protein * without micro-organism	14/21	9/21	15/21	8/21	6/21	6/21
5. Foreign Protein + Strep. + Pen. or S.A.D.or virus**	7/9	3/9	5/9	2/9	3/9	3/9
6. Strep. + Pen.	2/2	0/2	1/2	1/2	1/2	1/2
7. Microorganism with or without Foreign Protein***	9/11	3/11	6/11	3/11	4/11	4/11
T O T A L ****	23/32	12/32	21/32	11/32	10/32	10/32

* Foreign protein was horse serum in 17 instances. Albumin was injected in the other 4 rabbits, alone in two, and with S.A.D. in the other 2 animals.

** Foreign protein was albumin in the 2 animals that virus (vaccinia) was used, and with streptococci in one.

*** Foreign protein was horse serum in 6 animals.

**** Foreign protein was horse serum in 23 animals and albumin in 7.

horse serum and penicillin. The most severe reactions were found in the valvular endocardium and the myocardium of animals in the group injected with horse serum and streptococci which had been inactivated by penicillin or sulfadiazine.

The purpose of Experiment 2 was to learn whether crystalline egg albumin could serve for sensitization as effectively as horse serum.

Experiment 2. - Seven rabbits were employed, as outlined for Experiment 1. The histologic studies revealed alterations in all 7 animals. The involvement was most marked in the valvular tissues of 7 out of 7 animals and more extensive than in other areas. Mural endocarditis, myocarditis, percarditis, and arteritis were present in from 2 to 4 of the animals. From the results of Experiment 2 it was evident that the cardiovascular changes brought about by the use of horse serum alone, or in combination with streptococci, could also be elicited by albumin as the foreign protein.

Series A, which is summarized in Table I, demonstrated that either of the two foreign proteins, horse serum or egg albumin, alone, or in combination with streptococci, was effective in bringing about inflammatory changes in the cardiovascular system. The evidence to support the thesis that either of these agents in combination with streptococci served to potentiate the tissue alterations resulting from sensitization to streptococcal constituents was equivocal at best. It is of interest to point out that a mixture of streptococci and penicillin in the absence of a foreign protein was effective in bringing about tissue changes in the two animals which served as controls.

Series B. Monkeys

Series B, employing monkeys as the host species, was undertaken so as to confirm the findings which had been obtained in Series A and, more especially, to learn whether changes in the cardiovascular system similar to rheumatic fever in man could be elicited by employing a primate. The plan of procedure was the same as that described for Series A, except that each animal received more injections of the test agents.

Experiment 3. - The materials employed for inoculation, the number of monkeys utilized as recipients for each inoculum, and the results are presented in Table II.

The results of Experiment 3 are summarized in Table III. It can be seen that cardiovascular lesions were present in 14 of the 16 animals. Periarteritis, myocarditis, and valvular endocarditis were most common. The animals that received streptococci in combination with a foreign protein appear to have developed a significantly greater number of lesions with more extensive alterations than the animals that were given foreign protein without microorganisms. It was apparent from this experiment that the tissue changes of the monkey to the streptococcus were more extensive and that this response more nearly simulated that observed in rheumatic fever in man.

Experiment 4. - The possibility that the lesions observed in the monkey might represent an exaggeration of a spontaneous disease led us to study microscopically the tissues from each monkey that died accidentally or from a known noninfectious cause. Sections were prepared from 7 selected areas as designated by Gross, et al[32]. The findings for the monkeys from the University of Minnesota colonies are presented in Table IV.

It can be seen from Table IV that changes were minimal, shown in two of 8 animals, designated in this summary as myocarditis and pericarditis but actually limited to several small foci of mononuclear cells, whereas none showed evidence of endocarditis, arteritis, or periarteritis.

Experiment 5. - The hearts from 9 monkeys were obtained from Cincinnati, Pittsburgh, and Columbia, South Carolina,

Table II

EXPERIMENTAL CARDIOVASCULAR DISEASE IN MONKEYS

	ENDOCARDITIS		MYO-CARDITIS	PERI-CARDITIS	ARTERITIS	PERI-ARTERITIS
	Valvular	Mural				
Horse Serum	2/2	0/2	2/2	1/2	1/2	2/2
H.S. + S.A.D.	2/2	1/2	2/2	1/2	0/2	1/2
H.S. + Pen. + Strep. Super.	1/1	0/1	0/1	1/1	1/1	1/1
H.S. + Strep. + S.A.D.	1/2	0/2	2/2	1/2	2/2	2/2
H.S. + Strep. + Pen.	6/7	3/7	6/7	4/7	4/7	7/7
Strep. + Pen.	1/1	0/1	0/1	1/1	1/1	1/1

Table III

EXPERIMENTAL CARDIOVASCULAR DISEASE IN MONKEYS

	ENDOCARDITIS		MYO-CARDITIS	PERI-CARDITIS	ARTERITIS	PERI-ARTERITIS
	Valvular	Mural				
Streptococci with or without Foreign Protein*	8/10	3/10	8/10	6/10	7/10	10/10
Foreign Protein without Micro-organism	5/6	1/6	5/6	3/6	2/6	4/6
T O T A L	13/16	4/16	13/16	9/16	9/16	14/16

* Foreign protein was horse serum in 15 animals, and it was albumin in the other monkey.

Table IV

CONTROLS FOR CARDIOVASCULAR DISEASE IN MONKEYS

(Colonies at University of Minnesota)

Ref. #	Dept.B.& I.	ENDOCARDITIS		MYO-CARDITIS	PERI-CARDITIS	ARTERITIS	PERI-ARTERITIS
Source	U. of Minn.	Valvular	Mural				
Uninoc.							
Dept.B.& I.							
Hanged self	XP 318	0	0	0	0	0	0
Killed by bully	198	0	0	Min. 1+	Min. 1+	0	0
1 Rt.Cnl. Ther.	319	0	0	2+	0	0	0
		0/3	0/3	2/3	1/3	0/3	0/3
Ped. Res. (May)							
Vit.C. & Fol.Ac.Def.							
Babies	XP 28	0	0	0	0	0	0
	47	0	0	0	0	0	0
Immature (#16 & #6)	196	0	0	0	0	0	0
	197	0	0	0	(Min.±)	0	0
Mature	23	0	0	0	0	0	0
		0/5	0/5	0/5	1/5	0/5	0/5
T O T A L U. OF MINN.		0/8	0/8	2/8	2/8	0/8	0/8

Table V

CONTROLS FOR CARDIOVASCULAR DISEASE IN MONKEYS

(Referred from Other Colonies)

Ref. # / Source	Dept.B.& I. / U. of Minn.	ENDOCARDITIS Valvular	ENDOCARDITIS Mural	MYO-CARDITIS	PERI-CARDITIS	ARTERITIS	PERI-ARTERITIS
Uninoc.							
Cinn. N.Rh. (Sabin)	XP 105	0/1	0/1	0/1	0/1	0/1	0/1
Pitt.#1-6 (Salk)	XP 260-265	Min.1/6	0/6	0/6	0/6	0/6	0/6
Okatie Farms Hurt in fall	XP 431	0	0	0	0	0	0
Hurt in fight	432	0	(Min.±)	(Min.±)	0	0	0
		0/2	1/2	1/2	0/2	0/2	0/2
Total Other Col.		1/9	1/9	1/9	0/9	0/9	0/9
Total U. of Minn.		0/8	0/8	2/8	2/8	0/8	0/8
TOTAL OVERALL		1/17	1/17	3/17	2/17	0/17	0/17

Note: Positive findings, changes exceeding ±, were limited to 3 of 17 animals in control group.

for histologic examination as outlined for Experiment 4. The results of these studies were presented in Table V.

It can be seen from Table V that 1 out of the 9 monkeys had minimal changes, as shown by a few mononuclear cells in the mural endocardium and in the myocardium.

The total of the findings for the control series is included in Table V. Since changes were minimal, the extent limited to 3 out of 17 animals, the results are strikingly different from the findings that were summarized for the experimental disease in monkeys.

ROLE OF HOST: MAST CELLS

The role of the host in the production of changes of the rheumatic type is being investigated by histochemical means. The object was to study the relationship of age and species to tissue susceptibility. For the present, observations will be limited to two phases of this study, the distribution of metachromatic changes and the occurrence of mast cells.

Metachromasia reflects the presence of mucoproteins of high molecular weight containing sulfur. Hyaluronic acid and heparin are examples. It, therefore, is possible in the study of tissues by employing the dye, toluidine blue, to localize and to estimate the relative amount of mucoproteins in any given tissue. The studies of Altschuler and Angevine[33] of fibrinoid in so-called collagen diseases and personal observations of metachromatic substance in the walls of thickened musculo-elastic vessels in the subendocardium in rheumatic fever led us to explore the possibility that mast cells might play a role in the pathogenesis of rheumatic disease, especially since the reports of an increase in mast cells occurs in chronic inflammation of joints[34] and that mast cells in granulation tissue appear earlier and in increased number before diffuse metachromasia of the ground substance[35].

Procedure. - Material consisted of sections of 12 hearts from patients who died of active rheumatic fever and from a control series of 19 individuals in the same age groups, mostly children.* In addition to this human material, the hearts of 18 monkeys from 4 different colonies were studied. Sections were made from 7 selected areas of the heart in the human control and monkey groups, so as to have available for study the sites where Aschoff nodules were observed most frequently by Gross et al[32]. Alcohol fixation was employed for new specimens to eliminate the loss of the water-soluble granules of mast cells and other similar material in the stroma. Toluidine blue in alcoholic solution was employed as a stain to eliminate the possibility of false metachromasia.

RESULTS: - Metachromasia was observed as a prominent feature at the juncture of valvular tissues and underlying cardiac structures, at the juncture of endocardium with myocardium, in perivascular areas of the myocardium, in areas of pericardium which contained blood vessels, and commonly in the left auricle. The distribution of mast cells in the cardiac tissue followed this pattern. In some instances, the mast cells were seen in the delicate vascular spaces which are present in the network of the myocardial syncytium. It was observed that the distribution of Anitschkow cells[36,37] followed this over-all pattern.

The probability that cells with an Anitschkow configuration originate from mast cells has come to be entertained seriously. This deduction came about when it was observed repeatedly that cells designated as mast cells because of metachromatic cytoplasmic granules possessed nuclei with the linear bar of chromatin of firtree pattern, the type of nucleus that characterizes the Anitschkow cell. Further observations made it apparent

*Blocks of tissue for study were made available through the courtesy of the Department of Pathology at the University of Minnesota and the University of Kansas.

Table VI

MAST CELL COUNT IN CARDIAC TISSUES *

	M A N		M O N K E Y
	A.R.F.	Control	(Polio Test Group)
No. of Hearts Studied	12	19	18
Mast Cells	24	13	18

* Number of mast cells in 5 adjacent high power fields.

Table VII

ASSOCIATION OF MAST CELL GRANULES AND ANITSCHKOW TYPE OF NUCLEI

	M A N		M O N K E Y	TOTAL
	Rheumatic	Non-rheumatic	(Inj. c̄ Polio.Virus)	
No. of Hearts	12	19	18	49
Mast Cells with Anitschkow type of nucleus	26/10	14/6	13/5	53

that a series of intermediate transitional forms between the typical mast cell and the typical Anitschkow cell were present and especially common at the base of the initial and aortic valves and in thickened areas of the valves. Thus, in the absence of a recognizable cytoplasmic structure, nuclei of characteristic Anitschkow appearance were found in a fibrillar network of delicately pale metachromatic material. The latter change probably results from the disintegration of mast cell granules. Poorly outlined stellate cells with linear configuration of chromatin in the nuclei appear to be the intermediate forms. These forms were prominent at the base of the mitral and aortic valves and were present in the endocardium of the adjacent chambers of the heart and in thickened areas of the valves.

Of interest in support of the tenet that cells of the Anitschkow type derive from mast cells is the report of the extracardiac occurrence of the Anitschkow cell by Zak[38] and of our confirmation of these findings by the discovery of Anitschkow cells in focal accumulation in the muscular wall of the intestinal tract of a vitamin-C deficient monkey. Since these cells are not limited in occurrence to the myocardium, the more general distribution leaves open the possibility of origin from mast cells.

In an attempt to assess the relationship of mast cells to metachromasia and to Anitschkow cells, the mast cells were enumerated by the method of Janes and McDonald[34]. The hearts selected for study were representative of acute rheumatic fever, normal human hearts, normal monkeys, and from monkeys infected with poliomyelitis virus. The maximal and mean number of mast cells in five adjacent high-power fields were recorded for each case.

The results of these attempts to quantitate the mast cells are summarized in Table VI.

It can be seen from Table VI that the mean number in 5 adjacent high-power fields for 12 cases of acute rheumatic fever was 24; for the 19 control normal hearts, it was 13; and for the 18 monkey hearts, it was 18.

The relative numbers of Anitschkow cells and mast cells were proportional since the rheumatic hearts yielded mast cells with an Anitschkow type of nucleus in 26 instances in 10 hearts; for the normal control group, 14 instances in 5 hearts; and for the 18 poliomyelitis test monkeys, 13 instances of mast cells with the Anitschkow configuration were observed. These results are summarized in Table VII.

In summary, the Anitschkow type of mast cell was present in the hearts of all but two of the 12 representative of active rheumatic fever, whereas this type of cell was absent from 14 of 19 controls and from 13 of 18 monkeys.

SUMMARY

In an attempt to learn the reactivity of the cardiovascular system to the constituents of the streptococcus, normal animals and animals with an altered tissue reactivity brought about by hypersensitization with a foreign protein were injected repeatedly with hemolytic streptococci of Group A which had been inactivated *in vitro* by penicillin. This experimental approach thereby made it possible to learn the response of host tissues to the constituents of whole streptococci. Rabbits and monkeys were employed as the host animals. The animals were kept under observation for from two to eleven months, during which time they had repeated injections.

It was learned that streptococci alone or in combination with foreign proteins in normal and hypersensitized hosts were effective in bringing about inflammatory changes in the cardiovascular system. The histopathological changes observed ranged from an acute necrotizing process, changes suggestive of rheumatic disease with Aschoff-like nodules, to low-grade chronic inflammation. The most severe reactions were found in rabbits in the valvular endocardium and the myocardium. Cardiovascular lesions were present in

14 of the 16 monkeys employed. Periarteritis, myocarditis, and valvular endocarditis were most common. Monkeys that received streptococci had most consistently severe arterial or periarterial reactions. Since published results of studies designed to rule out spontaneous cardiovascular disease in this host species were not available, hearts from monkeys dead from accidental or other non-infectious agents were obtained from Cincinnati, Pittsburgh, and Columbia, South Carolina. The presence of minimal changes limited to a single one of these animals made our findings in the experimental group of more interest. Similar studies employing swine as the experimental host are under way.

In the second phase of this study, 49 hearts were studied by histochemical methods to assess tissues representative of naturally occurring rheumatic fever, non-rheumatic disease in man and normal monkeys and monkeys injected with poliomyelitis virus, so as to learn the relationship of metachromasia to activity and to the number and distribution of the mast and Anitschkow type of cells. The method of Gross was employed to quantitate the distribution of mast and' Anitschkow cells. Both types of cell apparently are related to activity in the rheumatic heart and in experimental disease. The observation repeatedly that cells ranging from typical mast cells with an abundance of granules, cells with loss of granules, and an increase of metachromasia of the tissues, nto total loss of granules and the presence of a linear chromatin bar in a nucleus such as characterizes the Anitschkow type brings up the probability that Anitschkow cells may derive from mast cells. Studies to learn the extra-cardiac occurrence of Anitschkow cells supported the belief that this is a cardiac cell.

The findings which are reported have been obtained in studies carried out over a period of three years in an attempt to learn something of the trigger mechanism and target in rheumatic disease.

It is believed that these results readily fit into past and current activities being carried out in this field at the University of Minnesota and elsewhere. Pioneer[39] and recent studies by Dr. Clawson of the reactions in rheumatic disease, and especially in experimental studies of normal, immune, and hypersensitive rabbits[40], have contributed much to our thinking of sub-acute bacterial endocarditis and rheumatic fever. He has stressed the importance of the factor of age[41]. The successful production of endocarditis involving the mitral and aortic valves in dogs following arteriovenous fistulae led Lillehei, Bobb, and Visscher[42] to emphasize the role of stress and the relationship of hormonal effects to the explosive phase. The target, i.e., the host, has been under investigation by Good and Glick[43], Kelley and Good[44], and others in their studies of the mucolytic enzyme systems and mucoproteins in blood.

Further studies utilizing the histochemical approach are in progress in cooperation with Dr. Charles F. Williams to associate the tissue reaction, especially mast cells[45,46,47,48], heparin, and adrenocorticotropic (ACTH) hormone in bridging the gap between the explosion and the target.

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** These experimental studies were in part carried out at Louisiana State School of Medicine, New Orleans, in collaboration with Dr. Harry E. Dascomb.

*** On leave of absence from University of Kansas School of Medicine, Kansas City.

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II. MEDICAL SCHOOL NEWS

Coming Events

January 26-28 - Continuation course in Pediatrics for General Physicians.

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

January 31 - J. B. Johnston Lecture - "Cortical Localization" - Fred A. Mettler, Columbia University; 8:00 p.m., Natural History Museum Auditorium.

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

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

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

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Faculty News

The Council of the Minnesota State Medical Association recently commended Dr. Owen H. Wangensteen, Director and Professor of the Department of Surgery, "for his invaluable contributions to medical research and practice."

A portion of the Council's citation, which was communicated to Dr. Wangensteen by Mr. R. R. Rosell, Executive Secretary of the Association, read; "The Council takes great pride in your accomplishments and the recognition of them and wishes to add its acknowledgment of your distinguished service to the profession and the public.

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National Conference on Cardiovascular Diseases

Members of the University of Minnesota faculty who will attend the National Conference on Cardiovascular Diseases in Washington on January 17-20, include Miss Katherine Densford, Director of the School of Nursing, Dr. Maurice Visscher, Professor of Physiology, and Dr. G. N. Aagaard, Director of Postgraduate Medical Education.

The Conference, which is sponsored by the National Heart Institute of the United States Public Health Service and the American Heart Association, will be divided into the following three sections: 1) Technical Knowledge and Research; 2) Community Services; 3) Professional Education.

The purpose of the Conference is "to investigate, define, and develop immediate and long-range programs designed to meet the problems of research, education, and community service posed by diseases of the heart and circulation; and to coordinate the efforts of all groups concerned with these problems, with a view to gaining the most effective use of their resources for all members of the community."

III.

UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
CALENDAR OF EVENTS

January 15 - January 21, 1950

No. 273

Sunday, January 15

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

10:30 - 11:00 Surgical Conference; Sulphathalidine with Uretero-Sigmoidostomy; Robert Evert; Rm. M-109, U. H.

Monday, January 16

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

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

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

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

11:00 - 11:50 Physical Medicine Seminar; Scoliosis in Poliomyelitis; Jose Montero; E-101, U. H.

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

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

12:00 - 1:00 Physiology Seminar; Observations on Gastric Secretion of Radioiodide; Henry S. Bloch and Edward E. Mason; 214 M. H.

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

12:30 - 1:20 Pathology Seminar; Hormonal Assays; Ellis Benson; 104 I. A.

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

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

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

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

4:00 - Pediatric Seminar; Erythroblastosis Fetalis; William Heilig; 6th Floor West, Child Psychiatry, University Hospitals.

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

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

Tuesday, January 17

8:15 - 9:00	Roentgenology-Surgical-Pathological Conference; Craig Freeman and L. G. Rigler; M-109, U. H.
8:30 - 10:20	Surgery Conference; Small Conference Room, Bldg. I, Veterans Hospital.
9:00 - 9:50	Roentgenology Pediatric Conference; L. G. Rigler, I. McQuarrie and Staffs; Todd Amphitheater, U. H.
10:30 - 11:50	Surgical Pathological Conference; Lyle Hay and E. T. Bell; Veterans Hospital.
12:30 -	Pediatric-Surgery Rounds; Drs. Stoesser, Wyatt, Chisholm, McNelson and Dennis; Sta. I, Minneapolis General Hospital.
12:30 - 1:20	Pathology Conference; Autopsies; J. R. Dawson and Staff; 102 I. A.
1:30 - 2:30	Pediatric Psychiatry Conference; R. A. Jensen and Staff; 6th Floor, West Wing, U. H.
1:00 - 2:30	X-ray Surgery Conference; Auditorium, Ancker Hospital.
2:00 - 2:50	Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III, Veterans Hospital.
3:15 - 4:20	Gynecology Chart Conference; J. L. McKelvey and Staff; Station 54, U. H.
3:30 - 4:20	Clinical Pathological Conference; Staff; Veterans Hospital.
4:00 - 5:00	Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.
5:00 - 6:00	X-ray Conference; Presentation of Cases by University Hospital Staff; Todd Amphitheater, U. H.
5:00 - 6:00	Porphyrin Seminar; C. J. Watson, Samuel Schwartz, et al; Powell Hall Amphitheater.
8:00 -	Minnesota Pathological Society; Psychosomatic Medicine - Present Day Concepts; Don Hastings; Medical Science Amphitheater.

Wednesday, January 18

8:00 - 8:50	Surgery Journal Club; O. H. Wangensteen and Staff; M-109, U. H.
8:30 - 9:30	Clinico-Pathological Conference; Auditorium, Ancker Hospital.
8:30 - 10:00	Orthopedic-Roentgenologic Conference; Edward T. Evans; Room 1AW, Veterans Hospital.
8:30 - 12:00	Neurology Rehabilitation and Case Conference; A. B. Baker; Veterans Hospital.
11:00 - 12:00	Pathology-Medicine-Surgery Conference; Surgery Case; O. H. Wangensteen, C. J. Watson and Staffs; Todd Amphitheater, U. H.
12:00 - 1:00	Radio-Isotope Seminar; Report of Recent Literature; O. M. Caudill, H. Katzovitz, and J. Friedman; 113 Medical Sciences.
3:30 - 4:30	Journal Club; Surgery Office, Ancker Hospital.

Wednesday, January 18 (Cont.)

4:00 - 5:00 Infectious Disease Rounds; General Hospital, Basement Amphitheater.

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

Thursday, January 19

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

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

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

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

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

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

12:00 - 1:00 Physiological Chemistry Seminar; Physiological Chemistry of Staining with Basic Dyes; Bo Malmstrom; 214 M. H.

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

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

4:15 - 5:00 Bacteriology and Immunology Seminar; Experimental Studies in Cardiovascular Disease - Rheumatic Type; Tom H. Hamilton; 214 M. H.

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

5:00 - 6:00 X-ray Seminar; New X-ray Procedures in the Diagnosis of Congenital Heart Disease; Joseph Jorgens; Todd Amphitheater, U. H.

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

Friday, January 20

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

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

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

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

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

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

Friday, January 20 (Cont.)

11:45 - 12:50 University of Minnesota Hospitals General Staff Meeting; The Value and Limitations of Heart Catheterization in Congenital Heart Disease; John W. LaBree; Powell Hall Amphitheater.

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

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

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

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

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

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

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

4:15 - 5:15 Electrocardiographic Conference; G. N. Aagaard, Reuben Berman, and Ernst Simonson; 106 Temp. Bldg., Hospital Court, U. H.

5:00 - 6:00 Otolaryngology Seminar; Review of Current Literature; Dr. Bofenkamp - Discussor, Dr. Connor; Todd Memorial Rm., U. H.

Saturday, January 21

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

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

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

9:00 - 11:30 Psychiatry Conference; Management of Chronic Outpatient Patient; Howell; Powell Hall Amphitheater, U. H.

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

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

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

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

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

11:00 - 12:00 Anatomy Seminar; Effects of Injury on the Cytoplasm and Dye-excretory Ability of Parenchymal Cells of the Dog Liver; W. Lane Williams; Bovine Metrorrhagia; A. F. Weber; 226 I. A.