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Treatment of Essential Hypertension

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I. HEXAMETHONIUM COMPOUNDS IN THE TREATMENT OF ESSENTIAL HYPERTENSION

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1. Introduction

Elevation of the blood pressure is best thought of as a symptom of disease and not a disease in its own right. It is probably merely a sign of some basic derangement, the identity of which, in the case of essential hypertension, is unknown. Drug therapy in the disorder has, to date, been primarily directed at lowering the blood pressure and the degree of lowering is taken as an index to the therapeutic efficacy of the drug. This is a very unsatisfactory, but unavoidable, state of affairs. Until we know the actual cause of essential hypertension we can scarcely do otherwise. Nevertheless, Hammarström (1947) has clearly demonstrated that, even in patients with severe essential hypertension, there is very considerable variation in the blood pressure level during any 24 hour period and that the term fixed hypertension is misleading. Also, rest in bed produces some decline in the blood pressure, especially during the first day or two, but even prolonged rest in bed does not abolish the 24-hour variation.

The profession has quite rightly developed a rather critical attitude toward new depressor agents since so many have come and gone without contributing much to the year-to-year management of patients with essential hypertension. Yet in spite of the fact that we know we are not treating the basic disorder in essential hypertension by the use of depressor agents, few will deny the need for a really effective one. After all, many of the worst sequelae of the disorder, such as cardiac failure, cerebrovascular accidents, and the unduly rapid progress of arteriosclerosis are due, at least in part, to the prolonged elevation of the blood pressure. The hexamethonium compounds have been introduced in the hope that they will fill the need for an effective depressor drug. Whether they do, or do not, ultimately prove to be of value they are sufficiently promising to merit close scrutiny at the present time. At the very least, they represent a step along the path that will almost certainly lead us to a clinically useful method of treating hypertension.

2. Ganglionic blocking agents in the treatment of essential hypertension.

A. Tetraethylammonium compounds.

The ability of quarternary ammonium compounds to block autonomic ganglia was investigated some 35 years ago by Burn and Dale (1915), who studied both tetramethyl- and tetraethylammonium salts. Since that time various refinements have been worked out, the most significant of which was, until recently, the further investigation of tetraethylammonium bromide by Acheson and Moe (1946). These drugs enjoyed a popularity among research workers that has not yet completely subsided. In animals, they exert a transitory depressor effect which was found not to be due to action of the drug on the heart, vascular smooth muscle, or vasomotor center. Page (1949) suggested that the mammalian response to tetraethylammonium compounds is a complex phenomenon due not only to autonomic ganglionic blockade but also to effects on the liver and adrenal medulla (since in large doses the drug may have a pressor effect). In human beings, Larsson and Frisk (1947) found that intravenous doses up to 10 mg. per kilogram produced a drop in blood pressure beginning 10 to 20 seconds after injection and reaching a maximum in 2 to 3 minutes. The depressor response was greater in hypertensive than in normotensive individuals and lasted no more than 30 minutes. Peripheral vasodilatation also occurred and lasted somewhat longer than the depressor effect. In one hypertensive patient, they were able to maintain the blood pressure at a near-normal level for 4 hours by constant intravenous infusion of the drug but the level rose rapidly as soon as the drug was discontinued. The results were con-

firmed and extended by Frisk, Hammarström, and others (1948) who found that the largest depressor effects were observed in hypertensive patients with the highest control pressures and that, in general, the older the patient the more likely he was to respond dramatically to the drug. They concluded from the latter observation that ". . . a noticeable fall in the systolic pressure and a relatively moderate fall in the diastolic pressure simultaneously with a slight increase or decrease in the pulse rate. . ." could be taken to indicate the presence of significant arteriosclerosis. Their findings with regard to the effects of the drug on hemodynamic factors other than the blood pressure are summarized below. The clinical possibilities of the tetraethylammonium compounds in the treatment of essential hypertension were severely limited by the very transitory nature of its depressor effect and, after a relatively brief period, workers in the field seem to have lost interest in them.

B. The Hexamethonium Compounds.

Hopes were again aroused, however, when Paton and Zaimis (1948) discovered that certain derivatives of the polymethylene ω - bistrimethylammonium series, experimentally called C-5 and C-6, are able to block autonomic ganglionic transmission. They found that pharmacologically their effects are similar to those of the tetraethylammonium compounds but that they are 10 to 20 times as potent and their effects last 3 to 4 times as long. Within a short time, penta- (C-5) and hexamethonium (C-6) compounds were being tried in the treatment of essential hypertension (Smirk and Alstad, 1951; Turner, 1950; Saville, 1950) with reports that possessed one thing in common: the methonium compounds were superior to the tetraethylammonium group. Probably the most authoritative American opinion as to the clinical usefulness of parenteral hexamethonium is provided by Freis (1951) and colleagues (1952). They attributed remission in 6 patients with malignant hypertension to the drug but were unable to halt the progress of the disease in 3 others, all of whom had azotemia or uremia. They obtained prolonged reduction of the blood pressure in 6 patients with less severe essential hypertension but found that the hypotensive effect was unsustained in 6 others. They believe that the development of tolerance to the drug is the most important reason for failure and recommend relatively large, infrequent doses as a means of getting around the difficulty. Bechgaard and co-workers (1951), using the oral form of hexamethonium, were able to control a patient with malignant hypertension for 9 months and think that it may be useful in younger patients with severe forms of essential hypertension. Other studies (Fullerton and Milne, 1951; Locket et al., 1951) find the oral drug useless. Italian workers (Masini and Rossi, 1951) report preliminary results using a slowly absorbed parenteral preparation that exerts an effect for 6 1/2 hours. Smirk (1951) has used a slow, continuous injection of hexamethonium bromide for the management of hypertensive crises. In spite of the relatively large number of reports now appearing, no one, apparently, has been able to control blood pressure levels satisfactorily in essential hypertension for more than a few months with hexamethonium salts.

The most meticulous study of the effects of hexamethonium compounds on patients with essential hypertension comes from a group of Scandinavian workers headed by Werkö (1951). They compared the effects of the drug to Amytal and tetraethylammonium bromide. The latter 2 drugs were found to produce a depressor effect that was no greater than the lowest daily spontaneous reading obtained in the hypertensive patients studied. The depressor effect of hexamethonium was, however, considerably in excess of that produced by the other 2 drugs or by daily spontaneous variation. Their data permit a comparison of the hemodynamic effects in patients with essential hypertension of tetraethylammonium bromide and of hexamethonium bromide. They conclude that

the hexamethonium compounds probably produce a pooling of blood in systemic circuit but noted that tolerance to the drug develops so rapidly that it ". . . has little place in the routine treatment of hypertension."

TABLE 1

The Hemodynamic Effects of Tetraethylammonium (Frisk 1948) and Hexamethonium (Werkö 1951) Compounds in Patients with Essential Hypertension.

	TEA	HXM
Systemic BP	Decr.	Decr.
Pulmonary BP	Decr.	Decr.
Pulse rate	Incr.	?Incr.
Cardiac output	Decr. (sl.)	Decr. (sl.)
Systemic PR	Decr. (sl.)	Decr. (sl.)
Cardiopulmonary BV	Decr.	Decr.

The other new development as regards the therapeutic use of depressor drugs in patients with essential hypertension has to do with 1-hydrazino-phthalazine (C-5968), a compound that is thought to act on the hind or midbrain (Schroeder, 1952). It is currently being used alone and in combination with hexamethonium salts for the control of hypertension. The clinical potentialities of the compound are not yet clear.

3. Clinical Study at University Hospitals

The clinical study at this hospital is not yet far enough along to permit the establishment of firm conclusions and the present report is decidedly preliminary. The data are not extensive enough, and the therapeutic groups much too small, to warrant detailed statistical analysis. All this is for the future but the data in their present state provide ample reason for the maintenance of an active interest in the methonium group of drugs.

A. Case Material

Patients with relatively severe, sustained elevation of the blood pressure were chosen from the ward and clinic populations. A deliberate attempt was made to exclude patients with extremely labile hypertension since the difficulties in evaluating the effect of therapeutic agents in such patients is well known. According to the available evidence, all except one of the patients were suffering from the essential variety of hypertension. The patient in question ( ) probably has essential hypertension but also gives history of obstruction of the genito-urinary tract which was relieved by operation and which may be related to the development of hypertension.

Since the group is made up almost entirely of patients with severe forms of the disease, visual disturbances were present in an unusually large proportion (one-half). In less severe forms of the disease, one ordinarily expects visual difficulties to be rare and if the patient presents any complaint at all it is usually headache. The latter was

TABLE 2

Initial (Pretreatment) Findings on 18 Patients with Essential Hypertension.

Patient	Age	Sex	*Duration (Years)	Head-ache	Visual Dist.	Dyspnea	BUN (mg.)	X-ray	ECG	Eye-Grounds	BP Mm. Hg. Syst.	BP Mm. Hg. Diast.
.	45	F	10	?	-	+	16	GEN	LVS	III	210	140
.	49	M	1	+	+	+	34	GEN	LVS	III	260	170
.	58	M	1	+	+	+	15	LVE	LVS	III	210	122
.	18	M	8	+	-	-	14	NEG	NEG	I	190	118
.	52	M	½	-	+	+	14	GEN	LVS	IV	300	175
.	37	F	14	+	+	+	19	GEN	LVS	III	204	120
.	31	M	½	+	+	+	264	GEN	LVS	IV	200	120
.	47	M	3	+	-	+	14	LVE	LVS	III	250	160
.	50	M	7	+	+	-	34	LVE	LAD	IV	254	164
.	51	F	10	+	-	-	14	GEN	LVS	III	250	130
.	36	F	10	+	+	?	37	LVE	LVS	IV	250	160
.	45	M	4	+	-	+	36	LVE	LVS	III	250	150
.	38	F	8	+	+	-	15	LVE	LVS	IV	230	158
.	69	M	?	-	-	+	24	LVE	LAD	II	200	124
.	62	M	2	+	+	+	42	LVE	LVS	IV	210	130
.	53	F	10	+	-	+	17	LVE	LVS	III	220	115
.	42	F	8	+	-	+	18	GEN	LVS	II	200	120
.	54	M	1	-	-	+	20	LVE	LVS	III	204	130

* Duration refers to time elapsed since discovery of elevated blood pressure.

present in 14 of the 18 patients but was the sole complaint in only 2 of them. Dyspnea on exertion was present in about the same number as headache. Clinical evidence of diffuse cerebrovascular damage was noted in at least 4, and possibly in 5, of the patients. Other symptoms, not listed in Table 2, included anginal pain (5), orthopnea (3), ankle edema (3), and nausea (3).

The severity of the disease in the group can be judged from Table 2. It will be seen that one-third of the patients had Grade IV hypertensive retinopathy (including papilledema) as judged by the Keith and Wagener criteria. Nine patients (one-half) had severe retinal changes, including hemorrhages and/or exudate (Grade III) but did not show papilledema. Two had arteriosclerotic changes and focal arterial narrowing in the retinae while one had focal narrowing only.

Accepting 20 mg. per 100 cc. as the upper limit of normal for the BUN, 7 of the patients had azotemia on admission but only one ( ) had marked elevation of the BUN and clinical signs of uremia. Roentgenologic and electrocardiographic evidence of the effects of prolonged elevation of the blood pressure on the heart was present in all but one of the group.

B. Method and Drugs.

During the control periods the blood pressure was measured, with the patient supine, every 6 hours. In a few cases it was measured every 2 hours. During treatment with hexamethonium the usual practice was to measure the blood pressure every 2 hours and, in some instances, it was measured every hour. Most of the determinations were made by the nursing staff. The drugs used were hexamethonium dibromide (Vegolysin and Bistrium) for parenteral administration and hexamethonium bromide for oral administration. At first, subcutaneous initial doses of 50 to 100 mg. (about 25 to 50 mg. of hexamethonium ion) were used but one near disaster caused modification of the dosage so that the standard initial dose is now 15 mg. If there is insufficient depressor response, the next dose is 25 mg., the next 50 mg. (given 3 hours apart), and so on until the effective dose is reached. Thereafter, the dose is probably best given every 6 or 8 hours although in some cases it was given every 4 hours. The oral preparation was given in 250 mg. doses every 4 to 8 hours at first but was increased to 2 to 3 times this amount if the response was unsatisfactory.

The ideal conditions, previously mentioned, for evaluating the therapeutic efficacy of depressor agents in essential hypertension were by no means fulfilled in the present study. In the first place, adequate hospital control periods are almost impossible to achieve in an institution of this type since financial factors are of major, if not primary, importance. It seems unreasonable, however, to discard the results of the study because the average stay of the patients in the hospital before treatment with hexamethonium was begun was a mere 8.7 days. As shown by Hammarström, most of the lowering of blood pressure attributable to hospitalization alone occurs within a few days after the patient is admitted. Further, the magnitude of the depressor effect produced by hexamethonium considerably exceeds anything that might be expected from hospitalization alone in a group of severely hypertensive patients of this type. This is not to say, however, that control periods such as those that were imposed on us by the circumstances in the present instance are fully satisfactory. It was also difficult to control certain other variables; some of the patients received mild sedation during the control period while others did not. The degree of activity allowed was severely limited in some patients and only moderately in others. Special tests which may depress the blood pressure, such as the sodium amytal and benzodioxane procedures, were done during the control periods in some of the patients. Sphygmomanometric readings taken during the 24 hours immediately following such studies were, however, omitted from our calculations. In the

face of all this, we are forced to regard slight or moderate changes in blood pressure following the institution of treatment with the test substance in an individual case with considerable caution, although changes for the group as a whole undoubtedly have more significance.

In appraising results such as these, one should immediately distinguish between long-term and immediate effects. Since none of our patients have received hexamethonium compounds for months or years, we can say nothing with regard to the long-term effects of the drug although a few inferences are perhaps permissable (see below).

TABLE 3

Comparison of Control (Pretreatment) and Lowest Daily Average Blood Pressure Levels during Treatment in 17 Patients with Severe Essential Hypertension.

	Average Blood Pressure in Hospital			
	Pretreatment		Lowest daily average (12-24 readings) during treatment	
	S	D	S	D
	222	143	165	101
	229	144	182	124
	186	132	154	110
	221	140	112	78
	202	130	160	106
	229	160	160	118
	208	133	110	70
	193	125	164	110
*	246	130	132	82
	251	162	158	106
	242	153	160	100
	248	156	146	94
	210	130	175	105
	225	141	168	108
	197	126	176	112
	177	111	142	88
*	193	119	162	102
Average	275	136	155	101

*Also received 1-hydrazino-phthalizine

As regards the immediate effects of the drug on the blood pressure, the results seem fairly conclusive. Table 3 shows the definite depressor effect of the parenteral form of hexamethonium. The table shows the difference between the average reading during the control period and the lowest day's average during the treatment period. Handled in this way, the data show that the average drop in systolic pressure was 120 mm. Hg., and that the corresponding value for the diastolic pressure was 35 mm. Hg. Although this is one of the favorite ways for handling sphygmomanometric data in therapeutic studies, it is to a large extent an invalid one. Some authors, for that matter, compare control readings with the lowest single reading obtained during treatment. Such methods, however, ignore the obvious fact that a single reading, or the average of multiple readings taken on any one day, are not very significant in the lives of patients with a form of hypertension that usually lasts over a period of many years. Table 3 does, nevertheless, tell us one rather significant fact: hexamethonium, like many other depressor agents, influences the systolic pressure considerably more than the diastolic. Somewhat more to the point are the data in Table 4.

TABLE 4

Effect of Parenteral Hexamethonium on Blood Pressure in 12 Patients with Essential Hypertension.

	Control Period (Days)	Treatment Period (Days)	Average Control BP		Average BP During R_x		Average Change		Average Daily Dose (Mg.)
			S	D	S	D	S	D	
	9	12	229	144	202	134	-27	-10	170
	6	6	222	143	190	117	-32	-26	88
	9	10	221	140	165	111	-56	-29	115
	25	12	202	130	181	118	-21	-12	80
	3	3	208	133	137	89	-51	-44	400
	6	5	229	160	183	140	-46	-20	143
	3	18	251	162	181	122	-70	-40	300
	10	11	242	153	171	112	-71	-41	40
	4	14	240	156	171	128	-69	-28	147
	11	5	225	141	174	112	-51	-29	100
	9	5	197	126	198	128	+ 1	+ 2	90
	16	3	177	111	147	83	-30	-29	77
Average	8.7	8.4	222	143	174	116	-46	-27	152

It shows that over an average treatment period of 8.4 days, parenteral hexamethonium, caused an average fall in systolic pressure of 46 mm. Hg. and of 27 mm. in the diastolic. Only one of the 12 patients included in the table failed to show a depressor response to parenteral hexamethonium. It will also be noted that there is only rough relation between the size of the total daily

dose and the degree of depressor response. The effect of the drug, viewed in this way, becomes much less dramatic than when judged by the data as arranged in Table 3. It is still considerable, however, and is particularly marked in patients having a very high control blood pressure level.

The oral drug appears to be somewhat less effective than the parenteral (Table 5). It was used alone in only 4 patients and was continued after discharge in 3. In this small group, it apparently produced a small decline in blood pressure in hospitalized patients but was not effective in holding the blood pressure at the lower levels for any considerable period of time after discharge. With so few cases, however, we can hardly begin to evaluate the oral form of the drug and are in the process of setting up larger series of cases in order to compare the parenteral and oral types.

TABLE 5

Effect of Oral Hexamethonium on 6 Patients with Essential Hypertension.

	Control Period (Days)	Treatment Period (Days)	Average Control BP		Average BP During $\bar{R}_x$		Average Change		Average Daily Dose (Mg.)
			S	D	S	D	S	D	
.	3	9	186	132	166	121	-20	-11	1625
.	16	14	177	111	154	84	-23	-27	473
*	14	5	171	128	181	130	+10	+ 2	1100
* .	5	10	183	140	174	124	- 9	-16	1375
.	5	13	215	120	172	102	-43	-18	875
.	4	5	210	130	186	116	-24	-14	602
Average	6	9	190	127	176	113	-18	-14	1008

*Patients received Parenteral Hexamethonium before Oral Preparation.

Much the same situation prevails with regard to the use of hexamethonium in combination with 1-hydrazino-phthalizine. The 2 drugs in combination have produced a depressor effect over periods of from 3 to 9 weeks in 4 patients but whether the combination is more effective than parenteral hexamethonium alone is not yet clear.

The foregoing, dealing entirely with the effects of the drugs on the blood pressure alone, is by no means the whole story. Symptomatic improvement was the rule rather than the exception. Of the 14 patients with headaches before the beginning of treatment, 10 obtained complete or almost complete relief from the symptom. In 3 of these, headache promptly returned when the drug was withdrawn. Improvement as judged by disappearance of dyspnea on exertion is impossible to guage in the series. As would be expected from the relatively short periods of treatment, there have been no impressive changes in electrocardiograms or roentgenograms of the heart. Of the 6 patients with definite papilledema before treatment, 4 showed ophthalmoscopic improvement in the papilledema disappeared coincident with the fall in blood pressure. In 2 of these, fresh retinal

hemorrhages also disappeared. It would be unduly sanguine, however, to maintain that the course of the hypertensive process in these 6 patients with papilledema has been drastically altered. One of them (_ _), who had very fulminating malignant hypertension by any standards, showed a very gratifying depressor response to parenteral hexamethonium and certainly became less dyspneic while receiving the drug. He went on to die, nevertheless, 3 days after the drug was started. Another patient with papilledema, a woman (... ..), showed very definite ophthalmoscopic and symptomatic improvement along with a moderate depressor response on parenteral hexamethonium but failed to maintain the improvement when put on the oral form of the drug. Another woman (_. _.) improved ophthalmoscopically and lost her headaches but later succumbed during bilateral adrenalectomy. She was treated with hexamethonium at a time when supplies of the drug were irregular, but graphic representation of her average daily blood pressures shows quite clearly that the levels repeatedly rose and fell as the drug was administered and withdrawn. The other 3 patients who had papilledema on admission are perhaps better than they were before treatment but nothing approximating dramatic improvement or cure can be claimed for them.

Some untoward effects of the drug in both its oral and parenteral forms are the rule rather than the exception but in our hands they have not as yet been serious. All patients receiving the drug parenterally suffered from dizziness on changing from the supine to the erect positions. Two patients fainted under these conditions. One patient ( ), who had evidence of diffuse cerebrovascular disease initially, became disoriented while receiving hexamethonium and the drug had to be discontinued. Nausea was also experienced by several patients along with postural dizziness. Some degree of constipation and abdominal distension was noted in 7 patients but frank ileus did not occur although it has been reported by others.

The possibility that hexamethonium therapy may cause a rise in the BUN of hypertensive patients was considered but review of the entire series does not bear this out. A rapidly rising BUN before treatment was seen in the patient with fulminating malignant hypertension ( ) and hexamethonium treatment did not halt the rise although the depressor response was excellent. In the rest of the patients there was no significant change in the BUN at the beginning and end of treatment.

4. Summary

It seems reasonable to state that parenteral hexamethonium compounds are relatively non-toxic depressor drugs that are effective in some measure in almost all patients with essential hypertension. Their action is considerably more prolonged than that of their predecessor, tetraethylammonium chloride, and it is perfectly feasible to give them over relatively long periods of time. Some degree of tolerance to the drug probably develops, however, and the fact is a serious limitation to its use in the long-term management of essential hypertension. Parenteral hexamethonium is without the least doubt the drug of choice in the treatment of acute hypertensive crises (except possibly those associated with pheochromocytoma) and, all things considered, is the most promising depressor drug yet developed.

The oral form of the drug is less effective than the parenteral but has not been sufficiently tested for final evaluation.

In conclusion, it is still out of the question to speak of curing essential hypertension by means of drugs and the prospects for a convenient, safe way of controlling it by the use of drugs over long periods of time is not bright. One may, however, venture the hope that we are gradually arriving at anti-hypertensive measures which are somewhat comparable to those available for controlling diabetes mellitus. We still cannot cure

the latter disease but can usually control it to some extent by the adroit juggling of the types of insulin used, of the doses of insulin, and of the diet. So it may well become with essential hypertension. With the prospect of having several safe and effective depressor drugs at hand, and with the knowledge that depressor dietary measures can be safely applied for limited periods of time, effective long-term treatment of the disease may well become a reality. As the patient develops tolerance to one drug, another drug or combination of drugs may be substituted. Even if it turns out that the drugs must be given parenterally, the situation will be no worse than that confronting the severe diabetic. We may, in this way, be able to retard the development of the cardiovascular, and possibly the renal sequelae, of essential hypertension for very considerable periods of time. But the basic disorder underlying essential hypertension, whether it be physiologic, biochemical, psychiatric, or all 3, still escapes us. The development of new and more effective depressor drugs such as the hexamethonium compounds, is nevertheless most welcome, but however welcome such a step is, it is still a measure of expediency.

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II. MEDICAL SCHOOL NEWS

Coming Events

March 24-26	Continuation Course in Therapeutics for General Physicians
April 7-9	Continuation Course in Surgery for General Physicians
April 8	George E. Fahr Lectureship; "Coarctation of the Aorta," Dr. Robert E. Gross, Ladd Professor of Children's Surgery, Harvard Medical School, and Surgeon-in-Chief, Children's Hospital, Boston; Owre Amphitheater; 8:15 p.m.
April 14-19	Continuation Course in Proctology for General Physicians
April 17-19	Continuation Course in Obstetrics for Specialists
April 21-23	Continuation Course in Pediatrics for Specialists

* * *

Dr. May to Leave

Dr. Charles D. May, Associate Professor of Pediatrics, will take over on July 1, 1952, his new position as Professor and Head of the Department of Pediatrics at the Medical College of the State University of Iowa in Iowa City. He succeeds Dr. Phillip C. Jeans who is retiring. The Department of Pediatrics and the Medical School will greatly miss an outstanding clinician, research worker, and friend. We all join in offering our congratulations and in wishing him success in his new post.

Markle Award

The John and Mary R. Markle Foundation has announced that Dr. Leonard F. Peltier, Clinical Instructor, Division of Orthopedics, is one of the 21 recipients of the Markle scholarship in 1952. The scholarship pays a total of $30,000.00 over a five-year period. Dr. Peltier will devote a major share of his time to research in orthopedic surgery. He joins two other University of Minnesota Medical School faculty members as recipients of the Markle Award: Dr. George E. Moore, Assistant Professor, Department of Surgery, and Dr. Robert A. Good, Assistant Professor, Department of Pediatrics.

Faculty News

Dr. Leo G. Rigler, Professor and Head, Department of Radiology and Physical Medicine, will address the Washington, D. C. Radiological Society March 21 on the subject, "The Roentgen Demonstration of the Biliary Tract and Some Observations on the Vascular Bed of the Liver."

On March 13, Dr. C. J. Watson, Professor and Head, Department of Medicine, discussed "The Problem of Dissociation of Impairment of Liver Function in Liver Disease" at a seminar sponsored by the Upjohn Pharmaceutical Company at Kalamazoo, Michigan. On March 17 he delivered the Annual Alpha Omega Alpha address at Temple University, Philadelphia. His subject was, "Reflections on Some Contemporary Problems of Training After Graduation From Medical School.

Dr. Martin E. Feferman, who has been associated with the Department of Surgery since 1947 and who has been for the past year senior resident in Neurosurgery, has completed his fellowship training. On April 1, 1952, he will open his office in South Bend, Indiana, for the private practice of neurosurgery. His many friends at the University join in wishing him the best of luck.

III. UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
WEEKLY CALENDAR OF EVENTS

Physicians Welcome

March 24 - 29, 1952

Monday, March 24

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 Kremen, Moore, and Stenstrom, Todd Amphitheater, U. H.

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

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

4:00 - Pediatric Seminar; Treatment of Streptococcal Diseases; Lloyd Denny; Sixth Floor West, U. H.

4:30 - 5:30 Dermatological Seminar; M-346, U. H.

4:30 - Public Health Seminar; 15 Owre Hall.

5:00 - 6:00 Urology-Roentgenology Conference; C. D. Creevy, O. J. Baggenstoss, and Staff; Eustis Amphitheater.

Minneapolis General Hospital

7:30 - Fracture Grand Rounds; Dr. Zierold; Sta. A.

10:30 - 12:00 Tuberculosis and Contagion Rounds; Thomas Lowry; Station M.

11:00 - Pediatric Rounds; Franklin H. Top; 7th Floor.

12:30 - Surgery Grand Rounds; Dr. Zierold; Sta. A.

1:00 - X-ray Conference; Classroom, 4th Floor.

1:30 - Pediatric Rounds; Robert Ulstrom; 4th Floor.

Veterans Administration Hospital

9:00 - G. I. Rounds; R. V. Ebert, J. A. Wilson, Norman Shrifter; Bldg. I.

11:30 - X-ray Conference; Conference Room; Bldg. I.

Monday, March 24 (Cont.)

Veterans Administration Hospital (Cont.)

2:00 - Psychosomatic Rounds; Bldg. 5.

3:30 - Psychosomatic Rounds; C. K. Aldrich; Bldg. I.

Tuesday, March 25

Medical School and University Hospitals

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

9:00 - 12:00 Cardiovascular Rounds; Station 30, U. H.

12:00 - 1:30 Selected Topics, Permeability and Metabolism; Nathan Lifson; 129 Millard Hall.

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

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

4:30 - 5:30 Clinical-Medical-Pathological Conference; Todd Amphitheater, U. H.

Ancker Hospital

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

Minneapolis General Hospital

8:00 - Pediatric Rounds; Spencer F. Brown; 5th Floor.

10:30 - 12:00 Medicine Rounds; Thomas Lowry and Staff; Station F.

11:00 - Pediatric Rounds; Erling S. Platou; 7th Floor.

Veterans Administration Hospital

7:30 - Anesthesiology Conference; Conference Room, Bldg. I.

8:30 - Infectious Disease Rounds; Dr. Hall.

8:45 - Surgery Journal Club; Conference Room, Bldg. I.

9:00 - Liver Rounds; Drs. Nesbitt and MacDonald.

9:30 - Surgery-Pathology Conference; Conference Room, Bldg. I.

10:30 - Surgery Tumor Conference; Conference Room, Bldg. I.

1:00 - Surgery Chest Conference; T. Kinsella and Wm. Tucker; Conference Room, Bldg. I.

Tuesday, March 25 (Cont.)

Veterans Administration Hospital (Cont.)

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

3:30 - 4:20 Clinical Pathological Conference; Conference Room, Bldg. I.

Wednesday, March 26

Medical School and University Hospitals

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

8:00 - 9:00 Roentgenology-Surgical-Pathological Conference; Norman Jacob and L. G. Rigler; Todd Amphitheater, U. H.

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

12:30 - 1:20 Radio-Isotope Seminar; Dr. Traub; 12 Owre Hall.

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

5:00 - 6:00 Vascular Conference; Todd Amphitheater, U. H.

5:00 - 7:00 Dermatology Clinical Seminar; Dining Room, U. H.

7:00 - 8:00 Dermatology Journal Club; Dining Room, U. H.

8:00 - 10:00 Dermatological-Pathology Conference; Review of Histopathology Section; R. Goltz; Todd Amphitheater, U. H.

Ancker Hospital

8:30 - 9:30 Clinico-Pathological Conference; Auditorium.

3:30 - 4:30 Journal Club; Surgery Office.

Minneapolis General Hospital

8:00 - Pediatric Allergy Rounds; Lloyd Nelson; 4th Floor.

10:30 - 12:00 Medicine Rounds; Thomas Lowry and Staff; Station D.

11:00 - Pediatric Rounds; Franklin H. Top; 7th Floor.

12:30 - Pediatric Staff Meeting; Well Baby Clinics in Minneapolis; Sidney Scherling; 4th Floor Annex.

12:30 - EKG Conference; Boyd Thomes and Staff; 302 Harrington Hall.

1:30 - Pediatric Rounds; E. J. Huenekens and Robert Ulstrom; 4th Floor.

Wednesday, March 26 (Cont.)

Minneapolis General Hospital (Cont.)

2:00 - 4:00 Infectious Disease Rounds; 8th Floor.

4:00 - 5:00 Infectious Disease Conference; Classroom, 8th Floor.

Veterans Administration Hospital

8:30 - 10:00 Orthopedic X-ray Conference; Conference Room, Bldg. I.

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

2:00 - 4:00 Infectious Disease Rounds; Conference Room, Bldg. I.

4:00 - 5:00 Infectious Disease Conference; W. Spink; Conference Room, Bldg. I.

7:00 p.m. Lectures in Basic Science of Orthopedics; Conference Room, Bldg. I.

Thursday, March 27

Medical School and University Hospitals

8:00 - 9:00 Vascular Rounds; Davitt Felder and Staff Members from the Departments of Medicine, Surgery, Physical Medicine, and Dermatology; Heart Hospital Amphitheater.

9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

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

1:30 - 4:00 Cardiology X-ray Conference; Heart Hospital Theatre.

3:30 - Medicine-Pediatric Infectious Disease Conference; Heart Hospital Auditorium.

4:00 - 5:00 Physiology-Surgery Conference; Todd Amphitheater, U. H.

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

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

Minneapolis General Hospital

8:00 - Pediatric Rounds; Spencer F. Brown; 5th Floor.

8:30 - Neurology Rounds; William Heilig; 4th Floor.

11:00 - Pediatric Rounds; Erling S. Platou; 7th Floor.

1:00 - Fracture-X-ray Conference; Dr. Zierold; Classroom.

Thursday, March 27 (Cont.)

Veterans Administration Hospital

8:00 - Surgery Ward Rounds; Lyle Hay and Staff; Ward 11.

9:15 - Surgery Grand Rounds; Conference Room, Bldg. I.

11:00 - Surgery Roentgen Conference; Conference Room, Bldg. I.

Friday, March 28

Medical School and University Hospitals

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.

10:30 - 11:50 Medicine Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

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

11:45 - 12:50 University of Minnesota Hospitals Staff Meeting; The Portable Mass Spectrometer: Its Clinical Application in the Diagnosis of Carbon Dioxide Retention; Frederick H. Van Bergen; Powell Hall Amphitheater.

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

2:00 - 3:00 Dermatology and Syphilology Conference; Presentation of Selected Cases of the Week; H. E. Michelson and Staff; W-312, U. H.

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

3:30 - 4:30 Advanced Neurophysiology Seminar; E. Gellhorn; 111 Owre Hall.

4:00 - 5:00 Dermatology Seminar; W-321, U. H.

5:00 - Urology Seminar and X-ray Conference; Eustis Amphitheater, U. H.

Ancker Hospital

1:00 - 3:00 Pathology-Surgery Conference; Auditorium.

Minneapolis General Hospital

11:00 - Pediatric Rounds; Franklin H. Top; 7th Floor.

11:00 - Pediatric-Surgery Conference; Dr. Wyatt, Forrest Adams; Classroom, Sta. I.

12:00 - Surgery-Pathology Conference; Dr. Zierold, Dr. Coe; Classroom.

1:00 - 3:00 Clinical Medical Conference; Thomas Lowry; Classroom, Station M.

Friday, March 28 (Cont.)

Minneapolis General Hospital (Cont.)

1:30 - Pediatric Rounds; Robert Ulstrom; 4th Floor.

Veterans Administration Hospital

10:30 - 11:20 Medicine Grand Rounds; Conference Room, Bldg. I.

1:00 - Microscopic-Pathology Conference; E. T. Bell; Conference Room, Bldg. I.

1:30 - Chest Conference; Wm. Tucker and J. A. Meyers; Ward 62, Day Room.

3:00 - Renal Pathology; E. T. Bell; Conference Room, Bldg. I.

Saturday, March 29

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; I. McQuarrie and Staff; Eustis Amphitheater,

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. Wangensteen 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.

Minneapolis General Hospital

8:00 - Pediatric Rounds; George Lund; 5th Floor.

11:00 - 12:00 Medical - X-ray Conference; O. Lipschultz, Thomas Lowry, and Staff; Main Classroom.

11:00 - Pediatric Clinic; C. D. May and Floyd Denny; Classroom, 4th Floor.

Veterans Administration Hospital

8:00 - Proctology Rounds; W. C. Bernstein and Staff; Bldg. III.

8:30 - Hematology Rounds; P. Hagenaand E. F. Englund.