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Bulletin of the
**University of Minnesota Hospitals
and
Minnesota Medical Foundation**



**The Nutritional Role of
Intestinal Microorganisms**

BULLETIN OF THE
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I. THE NUTRITIONAL ROLE OF
INTESTINAL MICROORGANISMS^{a, b}

K. R. Johansson, M.D.

A. Introduction

The intestinal microflora represents a competitive ecological system which influences the nutrition of man and animals. Its mode of action, however, is obscure. Although some of the early workers¹ considered intestinal bacteria harmful under certain dietary regimens, it was suggested by Pasteur² that the intestinal microflora may be essential for life. Because modifications of the intestinal flora are known to affect the nutrition of man and animals, it is assumed that these microorganisms, in situ, elaborate growth substances as well as toxic products. Upon the introduction of small quantities of antibiotics and other bacteriostatic agents in the diet, such activities of the intestinal flora are altered with either a favorable or a detrimental effect on the host. An elucidation of the nature of antibiotic-induced alterations in the intestinal microflora of the rat should contribute to our understanding of the role played by these organisms in the nutrition of other animals and man.

B. Historical Development*

a This work was supported by research grants from the Microbiological Institute, National Institutes of Health, Public Health Service and from the Graduate School, University of Minnesota.

b The following students have participated in the experimental work: Glen E. Peterson, Elliot C. Dick and J. Melnykowycz. Certain aspects of this problem will be used by these students in partial fulfillment of the requirements of the Graduate School for advanced degrees.

* The literature on this subject is voluminous; hence many statements will be made without recognition of the source. A number of excellent reviews have appeared which furnish a more complete bibliography^{3,4,5,6}.

As a result of the early belief that a dominantly proteolytic intestinal microflora was detrimental to "proper" intestinal physiology, most of the early studies were concerned with the establishment and maintenance of an aciduric intestinal flora.⁷ An aciduric intestinal flora was accomplished by the use of high-carbohydrate, low-protein diets. Dietary lactose and dextrans are the most favorable carbohydrates for establishing an acid-forming flora.

The dominance of Lactobacillus bifidus in the intestine of the breast-fed infant has been a subject of considerable interest. Nature has provided the infant with a food which promotes the development within the large intestine of large numbers of an aciduric bacterium, concomitant with a high reducing sugar content and a low pH in the stool.⁸ Other than the fact that a low intestinal pH is needed for optimal absorption of calcium and phosphorus³, it is difficult to assess the importance for the infant of an aciduric intestinal flora typified by a specific lactobacillus. The fact that bovine milk does not favor L. bifidus and raises the intestinal pH is of further pertinence. In the adult, implantation of L. acidophilus may suppress intestinal "auto-intoxication," constipation and even ulceration⁹. Recently, György, et al.¹⁰ reported human milk to contain a factor which stimulated in vitro growth of L. bifidus. This factor, probably a polymer of acetylglucosamine, was most potent in colostrum and was 50 to 100 times as active in human milk as in cow's milk. Human semen, tears, saliva, gastric juice, amniotic fluid and purified blood group substances A and B were also good sources. Tomarelli, et al.¹¹ found this factor, in the form of hog gastric mucin, to stimulate the growth of rats fed a simulated human milk diet. (Rat's milk is a good source of this substance.) Perhaps this growth factor is responsible for maintaining the L. bifidus population in the infant's intestine.

The first demonstration of the nutritional importance of intestinal microorganisms was that of Osborne and Mendel¹² who noted the tendency of rats fed poor

rations, known now to be highly deficient in the B vitamins, to become coprophagous with ensuing beneficial effects on growth. It was noted further that such animals possessed a simple fecal microflora in contrast to the heterogeneous flora of rats fed a balanced ration. That intestinal microorganisms are capable of the synthesis of a growth factor was demonstrated by Cooper¹³ when he alleviated polyneuritis in pigeons by feeding alcoholic extracts of rats' and rabbits' feces. These extracts obviously were rich in thiamine. Since coprophagy is, at least under some circumstances, of nutritional value to the animal, and since the intestinal flora is influenced by the diet, it has been assumed that the intestinal flora provides the host with a non-dietary source of growth factors. However, the availability of such nutrients to the host is a question as yet not satisfactorily answered. It is known that microbial cells absorb and bind large amounts of the B vitamins and do not release all of the vitamins which they synthesize^{14,15}. Furthermore, the more fastidious species may have such a great demand for nutrients that they compete with the host for growth factors present in the intestinal lumen. A large portion of growth factors present in the intestine leave the body^{16,17}. In fact, the sites of greatest intestinal biosynthesis appear to reside within the colon and cecum^{4,5}. Thus, animals fed a diet deficient in a vitamin may develop a deficiency despite the fact that amounts of the limiting factor, sufficient to alleviate the deficiency, are found in the distal regions of the gut.

Another aspect of the problem is that of the "vitamin-sparing" action of the relatively insoluble carbohydrates, e.g., dextrans, starches and, to a lesser degree, lactose. Thus, it is easy to produce a vitamin B₆ deficiency in the rat by a dietary carbohydrate source of sucrose or glucose, whereas the use of dextrin or lactose prevents the symptoms of acrodynia¹⁸. This action, for most of the B vitamins, has been demonstrated experimentally in several animal species. The explanation for the sparing action

of the complex carbohydrates is that a residual amount of carbohydrate is available to stimulate microbial biosynthesis in the terminal portion of the intestinal canal; such appears not to be the case with the simpler dietary carbohydrates.

Until 1941, the only vitamins required by the rat when fed purified rations were vitamins A, D and E, pantothenic acid, thiamine, riboflavin, niacin, pyridoxine and choline. However, by incorporation of one of the poorly absorbed sulfonamides in the ration it was possible to produce a multiple vitamin deficiency in the rat which was corrected by para-aminobenzoic acid, biotin, folic acid and vitamin K¹⁹. At the same time, the animal's requirement for the other B-vitamins increased. The feeding of such drugs caused marked suppression in the numbers of intestinal lactobacilli and coliform bacteria. Hence, it was believed that the sulfonamide interfered with the microbial synthesis of vitamins in the intestine.

In 1946, Moore, *et al.*²⁰ obtained evidence of growth stimulation by streptomycin and sulfaguanidine in chicks fed purified rations. By 1950, a number of studies revealed the ability of many of the antibiotics to stimulate the growth of chicks, rats, mice, swine and calves^{6,21}. In many instances, however, growth was stimulated only when a deficient purified ration was employed. Also, some evidence relates antibiotic-induced growth stimuli to the suppression of subclinical infections²². Most explanations for the growth promoting action of antibiotics encompass the intestinal microflora. A number of studies reveal the intestinal flora of animals fed minute amounts of antibiotics (5 to 200 mg per Kg. ration) to be drastically altered. However, the total number of intestinal organisms is not reduced; rather, a pronounced reappportionment of the flora occurs. Thus, indirectly, there is a relationship between the intestinal flora and growth. The possibility that the effects of antibiotics on the intestinal microflora are unrelated to the growth response of the host has been suggested on the basis of inconclu-

sive evidence^{23,24}. Little is known of the metabolism of antibiotics and their degradation products, but it is possible that there is participation of these substances in metabolic reactions within the body of the animal. The effects of sustained antibiotic administration of human growth and nutrition have been largely ignored, although signs of vitamin deficiencies in human adults given therapeutic levels of antibiotics for long periods have been observed.²⁵

Another approach to the evaluation of the nutritional role of intestinal microorganisms is that of "germ-free" life studies. Although attempts have been made since 1895 to maintain experimental animals under conditions which prohibit the development of an intestinal flora, until recent years efforts to do so have been unsuccessful. Reyniers and collaborators at the University of Notre Dame have been fairly successful in maintaining rats and poultry under germ-free conditions for 1 and 2 complete generations, respectively²⁶. They noted that these animals often gained weight more rapidly than "conventional" animals. A further provocative observation is that the B vitamin content of cecal material and of the liver was almost identical to that of the "contaminated" controls fed the same sterilized ration²⁷. Recently, the Notre Dame group reported that the growth of germ-free turkey poults was not stimulated by dietary antibiotics while growth of the control animals was definitely enhanced²⁸. Since germ-free animals may grow faster than the "conventional" animal, Reyniers postulated that the genetic capacity for growth is realized only under conditions of an adequate diet and a germ-free alimentary canal. Therefore, he believes that antibiotics promote animal growth because germ-free life is stimulated by suppression of activities of intestinal microorganisms.

It appears from this cursory inspection of the problem that the importance of the intestinal microflora to animal nutrition is poorly understood. Until some of the factors operative in the in vitro heterogeneous microbial system

called the intestinal microflora are elucidated, no valid conclusions can be made. Certainly, under some conditions, the intestinal flora aids the host.

C. Experimental

Inasmuch as a number of investigators attribute the growth stimulating action of antibiotics to effects on the intestinal microflora, a detailed study of growth and the intestinal flora of the rat fed aureomycin was undertaken in the fall of 1950. Weanling albino rats of the Sprague-Dawley strain were used: males were employed in the first experiment and females were used thereafter.

1. Part I.

In the first study²⁹, a purified vitamin B₁₂-deficient diet containing a suboptimal level of methionine was employed. The basal ration contained isolated soybean protein (21.8%), sucrose (60%), L-cystine (0.2%), salt mixture (4%), hydrogenated vegetable fats (6%), corn oil (3%), cellulose (5%) and the usual fat- and water-soluble vitamins except for B₁₂. The supplements employed were vitamin B₁₂ (20 mcg/kg), DL-methionine (6 g/kg), aureomycin hydrochloride (100 mg/kg) and a combination of B₁₂ and aureomycin. Groups of 4 animals were fed these rations, ad libitum, for a 30-day period, during which time they were weighed periodically, and their fecal flora was quantitated by customary bacteriologic methods. Two groups of control animals were fed a stock ration, one receiving aureomycin at the same dietary level as the animals fed the semi-synthetic diets. Results of the growth of these animals are presented in table 1. One rat fed the basal diet (insufficient in methionine and deficient in B₁₂) died and 3 were killed on the 10th day when symptoms, not unlike those of a methionine deficiency, were apparent. The addition of aureomycin to the basal diet delayed the onset of these deficiency symptoms until the 19th day, whereupon these rats were killed. Vitamin B₁₂ and methionine were equally beneficial to growth when added to the deficient basal mixture. Aureomycin produced a growth stimulation when

Table 1

Effect of Aureomycin, Vitamin B₁₂ and Methionine on the Growth of Rats Fed a Vitamin B₁₂-deficient, Methionine-low Diet (Condensed from Johansson, et al.²⁹)

Ration	Average 30-day wt. gain (grams)
Basal	-8 ¹
Basal + aureo.	+4 ²
Basal + methionine	+40
Basal + B ₁₂	+49
Basal + B ₁₂ + aureo.	+55
Stock	+109
Stock + aureo.	+103

¹ One animal dead on 10th day; remaining 3 killed.

² All 4 animals killed on 19th day because of severe deficiency symptoms.

added to the B₁₂-supplemented diet. In fact, for the first two weeks, rats fed such a diet grew as well as the two stock ration control groups. Supplementation of the stock diet with aureomycin had no influence on growth.

In table 2 the influence of dietary aureomycin upon the fecal microflora is summarized. Except for the aerobic "plate count", there was a striking effect, readily seen as a function of time, on the population of various intestinal bacteria. Although such results are not included in the table, numbers of yeasts increased during the experimental feeding period. Aureomycin also exerted a considerable effect upon the cecal and ileal microflora, particularly among the enterococcus and lactobacillus groups.

Assay³⁰ of fresh fecal droppings from these rats for vitamin B₁₂ revealed

little effect, if any, by aureomycin on the concentration of this vitamin (table 3). However, it is interesting to note that feces from rats fed the B₁₂-free basal ration contained as great a concentration of this vitamin as the animals fed a B₁₂-fortified diet.

2. Part II

Because the intestinal microflora is considered to participate in the "vitamin-sparing" action of rations containing an antibiotic or a complex carbohydrate, e.g., dextrin, it was of interest to evaluate simultaneously the effects of dietary aureomycin and carbohydrate. This objective was accomplished by correlating growth with alterations of the intestinal flora and with amounts of the limiting vitamin, viz., vitamin B₁₂, in the intestine and certain tissues³¹. The basal ration used was identical to the former diet except

Table 2

Summary of Quantitative Fecal Flora Study of Rats Fed Purified
and Stock Diets Supplemented with Aureomycin
(Condensed from Johansson, et al.²⁹)

Type of Bacterium Counted	Ration	HOURS AFTER START OF AUREOMYCIN FEEDING				
		0	12	36	84	144
"Total" aerobes (x 10 ⁸)	Purified	9.6	45.3	22.4	16.1	27.8
	Stock	13.4	13.6	18.6	19.5	36.0**
Lactobacillus (x 10 ⁸)	Purified	43.0	2.4	2.8	3.8**
	Stock	45.0	42.5	23.0	0.9	1.0**
Aureo-resistant aerobes (x 10 ⁶)	Purified	5.1	4.9	370.0	192.5	266.3**
	Stock	4.6	21.9	78.0	219.5	700.0**
Coliforms (x 10 ⁶)	Purified	69.3	80.0	80.0	81.8	37.8
	Stock	6.7	80.0	80.0	670.0	625.0**
Aureo-resistant coliforms (x 10 ⁵)	Purified	0.0	24.3	70.3	380.0**
	Stock	0.06	0.08	0.4	2.4*
Enterococcus (x 10 ³)	Purified	0.1	90.0	90.0	140.0	825.0**

* Significant effect (p = <0.05)

** Highly significant effect (p = <0.01)

Table 3

The Vitamin B₁₂ Content (mg per gram, wet weight) of Fecal
Droppings from Rats Fed Various Rations
(From Johansson, et al.²⁹)

No. Days on Ration	RATION					
	Basal	Basal + aureo.	Basal + B ₁₂	Basal + B ₁₂ + aureo.	Stock	Stock + aureo.
1					2,700	1,110
2	950	190				
4	600	950	850		800	1,500
5	760	300	600	900	2,800	1,700
6	310	220				
16			1,290	1,030	1,790	590
20			620	620		

that 0.6% DL-methionine was added at the expense of protein. Also, one basal ration contained sucrose as the carbohydrate while dextrin was used in the other basal mixture. Both basal rations were supplemented with vitamin B₁₂ (25 mcg/kg) and/or aureomycin hydrochloride (100 mg/kg). Four weaning male rats were fed each dietary mixture (8 groups in all). Analyses were made, as before, of the fecal and intestinal flora. The

vitamin B₁₂ concentration was determined, at the end of the 42-day feeding period, in pooled samples of contents from the colon, cecum and ileum, and in renal and hepatic tissues³⁰. This time, however, the assay was performed so as to determine both "free" and "bound" forms of the vitamin³¹.

The growth and food efficiencies of these animals are summarized in table 4.

Table 4
Effects of Vitamin B₁₂, Aureomycin and Dietary Carbohydrate on Growth and Food Efficiency
(Condensed from Peterson, et al.³¹)

Ration	Avg. wt. gain ¹ (grams)	Avg. food eff. ² (per cent)
S(sucrose) basal	78.0	19.0
S + aureo.	98.3	21.2
S + B ₁₂	128.5	23.1
S + aureo. + B ₁₂	157.5	26.2
D(extrin) basal	102.3	21.1
D + aureo.	117.8	23.1
D + B ₁₂	135.3	21.4
D + aureo. + B ₁₂	152.5	26.2

¹ Avg. of 4 animals over 42-day period

² Food eff. = $\frac{\text{wt. gained}}{\text{food consumed}} \times 100$; avg. of 4 animals over 42-day period.

It is apparent that dextrin was superior to sucrose in supporting the growth of rats fed a ration deficient in vitamin B₁₂. Furthermore, aureomycin partially alleviated the growth depression resulting from a dietary deficiency of B₁₂. Maximal growth, however, was not secured by merely adding the limiting factor to the diet, since the inclusion of both B₁₂ and aureomycin in the ration induced greater weight gains than the singly-supplemented diets, particularly in the

sucrose-fed animals. The two supplements were approximately additive in their effects on growth and food efficiency.

Table 5 indicates the effects of aureomycin on the fecal microflora of the animals fed the sucrose-containing rations and of those fed the dextrin-containing diets. The effects of aureomycin on the fecal-flora of the dextrin-fed rats differed from those in animals

Table 5
Effects of Aureomycin on Fecal Bacteria in Rats Fed Purified Rations Containing Sucrose or Dextrin
(Condensed from Peterson, et al.³¹)

ORGANISM	SUCROSE GROUPS		DEXTRIN GROUPS	
	Initial popln.	Popln. 196 hrs. later	Initial popln.	Popln. 196 hrs. later
<i>Proteus</i> spp. (x 10 ⁴)	8.0 ¹	1,300	8.5	1,300
<i>Lactobacillus</i> spp. (x 10 ¹)	71.0	18	63.0	400
<i>Enterococcus</i> (x 10 ⁴)	0.1	40	0.4	560
<i>Clostridium perfringens</i> (x 10 ⁴)	0.4	89	45.0	1,000
Coliforms (x 10 ⁵)	40.0	140	19.0	1,300
Aureo. resistant bacteria (x 10 ⁶)	0.4	4,500	0.4	2,500

¹ Avg. no. per gram, fresh wt. feces

fed the sucrose diets by 1) a slight increase (instead of a decrease) in numbers of lactobacilli, 2) a greater increase in the coliform population, and 3) a considerably greater rise in numbers of *C. perfringens*. Most of these effects upon the flora were noted within 16 hours after initiation of aureomycin feeding. Effects of the antibiotic on the microflora within the cecum and ileum were also studied but these data are not tabulated here. In summary, the effects observed for the microflora from these two intestinal levels were similar to the findings for feces. It is of interest to note that in every case the rats fed aureomycin had enlarged ceca.

The intestinal and tissue concentrations of vitamin B₁₂ are listed in table 6. Regardless of the dietary supplement, the concentration of all "states" ("free," "bound" and "total") of intestinal B₁₂ increased in the following order: ileum, cecum, colon. The incorporation of vitamin B₁₂ in the diet was reflected, in the colon and cecum, by a rise of "free" B₁₂. Irrespective of the carbohydrate, the presence of aureomycin in the diet raised, to a highly significant degree (p = 0.007), the concentration of "free" B₁₂ in both the colon and cecum. The ileal level of "free" B₁₂ was raised by the antibiotic in the animals fed dextrin but not for rats given sucrose. It can be concluded that there was no relationship between the tissue and intestinal concentrations of vitamin B₁₂ in any of the dietary groups. The antibiotic had no influence on tissue concentrations of B₁₂ despite its sparing effect on growth. It should be pointed out, however, that the concentration of "free" vitamin B₁₂ in the colon and cecum increased indirectly with the growth-promoting capacity of the ration.

3. Part III

Some investigators have ascribed the growth-enhancing action of antibiotics to a suppression of intestinal

Table 6

Effect of Vitamin B₁₂, Aureomycin and Dietary Carbohydrate
on Intestinal and Tissue B₁₂ Levels in the Rat
(Condensed from Peterson, *et al.*³¹)

RATION	COLON		CECUM		ILEUM		TISSUE	
	Free ¹	Bound ²	Free	Bound	Free	Bound	Kidney ³	Liver ³
S(ucrose) basal	340 ⁴	900	53	1,107	135	177	76	48
S + aureo.	390	873	73	732	135	175	77	38
S + B ₁₂	605	1,135	520	435	255	62	1,153	313
S + aureo. + B ₁₂	1,150	660	760	660	190	83	1,225	201
D(extrin) basal	415	1,695	165	617	165	139	108	49
D + aureo.	570	1,570	740	262	650	156	103	37
D + B ₁₂	550	1,330	240	735	55	176	990	124
D + aureo. + B ₁₂	800	1,080	700	595	95	313	990	200

¹ That B₁₂ easily eluted with water.

² That B₁₂ not readily eluted with water but liberated by enzymatic digestion.

³ These determinations represent the "total" B₁₂ present in the tissue.

⁴ Millimicrograms per gram, fresh weight.

bacteria which produce toxic products in situ. One such group of compounds known to be produced by indigenous intestinal bacteria is amines, some of which are toxic in physiologic amounts. One should not ignore, however, the fact that some of the amines may be true growth factors.

A number of attempts to detect amino acid decarboxylase activity, by customary manometric methods, in fresh and dried fecal and intestinal preparations from rats fed a stock diet resulted in data which were essentially negative³². Slight decarboxylase activity was consistently found in fecal, colon and cecal material, and occasionally in contents of the ileum; contents of the proximal portions of the intestine uniformly were lacking in demonstrable decarboxylase activity. On the other hand, crude mixed cultures grown from fecal inocula

possessed very potent amino acid decarboxylases, depending on pH and oxygen tension. Table 7 summarizes the effects of pH, oxygen tension and aureomycin on the decarboxylase activity of mixed fecal cultures. Each of the media used contained glucose, tryptone and K₂HPO₄ in various proportions. Media A and B contained 0.05% Na thioglycolate but differed in that B contained a very low concentration of glucose. Medium C contained no reducing agent and even less glucose than B, and was sometimes supplemented with 1 mcg aureomycin/ml. It may be noted that anaerobiosis favored the formation of all amino acid decarboxylases tested except that specific for glutamic acid. A low pH during growth was stimulatory to all decarboxylases except for lysine which was inhibited and glutamic acid which was indifferent to pH. Medium A was the only one to favor histidine decarboxylase. Aureomy-

Table 7

Amino Acid Decarboxylation by Mixed
Fecal Cultures Grown under Various Conditions
(Condensed from Melnykowycz³²)

Medium	Final pH	Glutamic Acid	Arginine	Lysine	Tyrosine	Histi- dine
A (aerobic)	4.5	215 ¹	317	17	42	285
B (aerobic)	7.0	200	15	404	15	15
C (anaerobic)	7.0	44	57	189	108	0
C (aerobic)	7.2	83	20	0	0	0
C + aureo. (anaerobic)	6.4	24	22	0	0	0
C + aureo. (aerobic)	7.2	80	0	0	0	0

¹ microliters CO₂ evolved / mg cell nitrogen in 1 hour

cin inhibited the activity of all decarboxylases, although the glutamic acid enzyme was scarcely affected.

While it is apparent that the ability of intestinal bacteria to produce amines is not lacking, their capacity to do so in vitro might be questioned. Hence, an attempt was made to detect amines in feces and intestinal contents. This was successfully accomplished by concentrating acid-hydrolyzed material in vacuo, extracting with ether in a liquid-liquid extractor and demonstrating the presence of amines by paper partition chromatography according to the method of Bremner and Kenten³³. A number of amines were thus found, including agmatine, putrescine, tyramine, histamine, ethanalamine, ephedrine and an unidentified amine. Similarly, mixed fecal cultures also possessed these amines.

Having established the presence of

amines in the lumen of the intestine, it was of interest to determine the effect of dietary aureomycin upon the formation of intestinal amines. In rats fed a stock diet supplemented with aureomycin, only putrescine could be detected. Likewise, in mixed cultures aureomycin suppressed the formation of amines, as was predicted from the effects of this drug on amino acid decarboxylases (table 7). These results lend some support to the theory that the promotion of animal growth by dietary antibiotics results from a suppression of sub-clinical intestinal "auto-toxemia."

D. Discussion

These experimental observations, collectively, aid in an appreciation of the difficulties encountered when attempting to evaluate the role of the intestinal microflora. The mere demonstration of growth responses occurring concomitantly

with modifications of the intestinal flora leaves much for speculation. Thus, aureomycin stimulated the growth of rats fed diets deficient in vitamin B₁₂ and, at the same time, exerted a definite influence on the composition of the intestinal flora. What does this mean in terms of the nutrition of the host? Although much is known of the physiology of indigenous intestinal bacteria when cultivated in vitro as pure cultures, essentially nothing is known of the physiology of heterogeneous microbial systems. Certainly synergisms and antagonisms must function in a microflora as complex as that within the intestinal canal.

In addition to effects of aureomycin upon growth and the intestinal flora, this study has demonstrated that the availability of a limiting dietary factor may be enhanced by the feeding of an antibiotic. This was shown by the antibiotic-induced rise in "free" intestinal vitamin B₁₂ in animals on a B₁₂-deficient diet. Chow, et al.³⁴ recently demonstrated aureomycin and other antibiotics to raise the intestinal concentration of butanol-extractable B₁₂ in rats. The lack of any effect by aureomycin on tissue levels of vitamin B₁₂ is perplexing. Furthermore, with vitamin B₁₂ there is the involvement of Castle's "intrinsic factor" which presumably is not operative in aiding absorption of B₁₂ in the terminal synthesizing region of the intestine. Apparently, some small portion of the intestinally-synthesized B₁₂ was assimilated because of the good correlation between amounts of "free" B₁₂ in the cecum and colon and the growth response to aureomycin*. Until more is known of absorption of nutilites from the intestine, this dilemma cannot be resolved.

The demonstration in these animals

* A recent report³⁵ has indicated that a large share of the vitamin B₁₂ present in the rat's large intestine is in the form of B_{12f} which appears to be of no use to the animal. The E. coli strain used to assay for B₁₂ responds to this form of vitamin B₁₂.

of amine formation has revived the old subject of "ptomaines." The presence and physiologic significance of amines in the lumen of the intestine has been a subject of considerable investigation, particularly with respect to histamine and tyramine^{36,37}. Since the intestinal mucosa and other tissues contain amine oxidases, e.g., "histaminase," it was thought that amines are quickly destroyed³⁸. However, the young of most animals, including man, possess in their various tissues appreciably less active amine oxidase than does the adult^{39,40}. Hence, it is possible that toxic levels of amines may be encountered within the intestine of young animals, infants and children. On the basis of these preliminary results, it is suggested that aureomycin may suppress amine formation and thus enhance growth in young animals. Perhaps the preponderance of lactobacilli in the human infant also inhibits the intestinal formation of amines? This, however, is contrary to Gale's⁴¹ opinion that the decarboxylation of amino acids is useful in counteracting decreases in pH since a relatively low pH is necessary for optimal amino acid decarboxylase activity. It would seem from results with mixed fecal cultures that such is not always the case. Thus, lysine decarboxylase activity was considerably greater when these mixed cultures were grown at a pH near 7 than when grown under conditions of a much lower pH, while glutamic acid decarboxylase was not significantly influenced by pH during the growth of such cells. This might be a manifestation of the selection of those species endowed with the most potent amino acid decarboxylases, rather than a reflection of the pH most optimum for the formation of decarboxylases. On the basis of these results and ensuing hypotheses, it can be concluded that mixed microbial populations, as exist in the intestinal tract, may carry out biochemical transformations that are not predictable from the employment of pure cultures in the laboratory. In other words, synergisms may play an important role in the activities of the intestinal microflora.

It is premature to suggest the extent to which the intestinal flora influences

the nutrition of the host. Of this we are certain: the competitive ecological system which thrives within the intestinal canal is sensitive to numerous known and unknown factors, dietary and otherwise. If antibiotics exert their growth-enhancing property through effects upon the intestinal microflora, it can be concluded that organisms present in the intestinal canal are not particularly beneficial to the host. However, many studies have indicated otherwise. Moreover, antibiotics often do not enhance growth. Considerably more knowledge of the "normal situation" is needed before attempting to explain the growth effects of bacteriostatic agents.

E. Summary

1. The development of our knowledge of the significance of the intestinal microflora has been reviewed briefly. Although the bulk of the evidence would indicate a beneficial influence of the intestinal flora upon the host, this is by no means incontrovertible.

2. By feeding rations deficient in vitamin B₁₂ and/or insufficient in methionine to rats, orally-administered aureomycin was found to: 1) influence growth and food efficiency; 2) alter, in numerous respects, the intestinal microflora; and 3) raise the level of "free" vitamin B₁₂ in contents of the cecum and colon -- "total" B₁₂ in the liver and kidney was unaffected. Furthermore, aureomycin stimulated growth less in a dextrin-containing, purified, B₁₂-deficient diet than in an identical ration with sucrose as the sole dietary carbohydrate. The latter effect was undoubtedly a result of the vitamin B₁₂ "sparing action" exerted by dextrin.

3. Although amino acid decarboxylases of fecal and intestinal preparations were scarcely evident, a number of amines were recovered from the intestines of rats fed a stock diet. Upon the feeding of this ration supplemented with aureomycin, only one amine, viz., putrescine, could be demonstrated in the intestinal contents.

4. Mixed cultures derived from an inoculum of rat feces exhibited excellent

amino acid decarboxylase activity, dependent to a large extent upon the pH and oxygen tension during growth. When present in such mixed cultures, aureomycin inhibited all amino acid decarboxylases tested except that specific for glutamic acid; this was confirmed by finding an accompanying decrease in amine formation.

References

1. Metchnikoff, I. I.
The Nature of Man.
Putnam's Sons, N. Y. (English translation), 1905.
2. Pasteur, L.
Observations relatives a la note precedente de M. Duclaux.
Compt. rend. acad. sci., 100: 68, 1885.
3. Elvehjem, C. A. and Krehl, W. H.
Imbalance and Dietary Interrelationships in Nutrition.
J. Am. Med. Ass'n., 135: 279, 1947.
4. Elvehjem, C. A.
Nutritional Significance of the Intestinal Flora.
Fed. Proc., 7: 410, 1948.
5. Johansson, K. R. and Sarles, W. B.
Some Considerations of the Biological Importance of Intestinal Microorganisms.
Bact. Rev., 13: 25, 1949.
6. Braude, R., Kon, S. K. and Porter, J. W. G.
Antibiotics in Nutrition.
Nutrition Abstracts and Rev., 23: 473, 1953.
7. Rettger, L. F. and Choplin, H. A.
A Treatise on the Transformation of the Intestinal Flora with Special Reference to Implantation of Bacillus acidophilus.
Yale Univ. Press, New Haven, Conn., 1921.

8. Barbero, G. J., Runge, G., Fischer, D., Crawford, M. N., Torres, F. E. and György, P.
Investigations on the Bacterial Flora, pH and Sugar Content in the Intestinal Tract of Infants. *J. Ped.*, 40: 152, 1952.
9. Rettger, L. F., Levy, M. N., Weinstein, L. and Weiss, J. E.
Lactobacillus acidophilus and Its Therapeutic Application.
Yale Univ. Press, New Haven, Conn., 1935.
10. György, P., Kuhn, R., Norris, R. F., Rose, C. S. and Zilliken, F.
A Hitherto Unrecognized Biochemical Difference between Human Milk and Cow's Milk.
Am. J. Dis. Child., 84: 482, 1952.
11. Tomarelli, R. M., Linden, E., Durbin, G. T. and Bernhart, F. W.
The Effect of Mucin on the Growth of Rats Fed Simulated Human Milk.
J. Nutrition, 51: 251, 1953.
12. Osborne, T. B. and Mendel, L. B.
Feeding Experiments with Isolated Food-substances. I. and II.
Carnegie Inst. Wash. Pub., 156: 1; 55, 1911.
13. Cooper, E. A.
On the Protective and Curative Properties of Certain Food-stuffs Against Polyneuritis Induced in Birds by a Diet of Polished Rice. Part II. *J. Hyg.*, 14: 12, 1914.
14. Tompson, R. C.
Synthesis of B-Vitamins by Bacteria in Pure Culture.
Univ. Texas Pub. No. 4237: 87, 1942.
15. Oginsky, E. L.
Uptake of Vitamin B₁₂ by Escherichia coli.
Arch. Biochem. Biophys., 36: 71, 1952.
16. Mitchell, H. K. and Isbell, E. R.
Intestinal Bacterial Synthesis as a Source of B-Vitamins for the Rat.
Univ. Texas Pub. No. 4237: 125, 1942.
17. Denko, C. W., Grundy, W. E., Wheeler, N. C., Henderson, C. R., Berryman, G. H., Friedmann, T. E. and Youmans, J. B.
The Excretion of B-complex Vitamins by Normal Adults on a Restricted Intake.
Arch. Biochem., 11: 109, 1946.
18. Sarma, P. S., Snell, E. E. and Elvehjem, C. A.
The Vitamin B₆ Group. VIII. Biological Assay of Pyridoxal, Pyridoxamine and Pyridoxine.
J. Biol. Chem., 165: 55, 1946.
19. Daft, F. S. and Sebrell, W. H.
Sulfonamides and Vitamin Deficiencies. *Vitamins and Hormones*, 3: 49, 1945.
20. Moore, P. R., Evenson, A., Luckey, T. D., McCoy, E., Elvehjem, C. A. and Hart, E. B.
Use of Sulphasuxidine, Streptothricin, and Streptomycin in Nutritional Studies with the Chick.
J. Biol. Chem., 165: 437, 1946.
21. Stokstad, E. L. R.
Antibiotics in Animal Nutrition. *Antibiotics Chemother.*, 3: 434, 1953.
22. Coates, M. E., Dickinson, C. D., Harrison, G. F., Kon, S. K., Porter, J. W. G., Cummins, S. H. and Cuthbertson, W. F. J.
A Mode of Action of Antibiotics in Chick Nutrition.
J. Science Food Agric., 3: 43, 1952.
23. Elam, J. F., Jacobs, R. L., Tidwell, W. L., Gee, L. L. and Couch, J. R.
Possible Mechanism Involved in the Growth-promoting Responses Obtained from Antibiotics.
J. Nutrition, 49: 307, 1953.
24. Peterson, G. E. and Johansson, K. R.
Effects of Oral and Parenteral Administration of Degraded and Active Antibiotics to Rats Fed a Vitamin B₁₂ Deficient Ration. I. Growth and Intestinal Microflora. *Antibiotic Symposium, 1953 (in press)*.
25. Anonymous.
Vitamin Deficiency Signs During Antibiotic Therapy.
Nutrition Rev., 9: 283, 1951.

26. Reyniers, J. A., Trexler, P. C., Ervin, R. F., Wagner, M., Luckey, T. D. and Gordon, H. A.
Germ-free Life Studies.
Lobund Rept. No. 2. Univ. Notre Dame, 1949.
27. Reyniers, J. A., Trexler, P. C., Ervin, R. F., Wagner, M., Gordon, H. A., Luckey, T. D., Brown, R. A., Mannering, G. J. and Campbell, C. J.
Germ-free Chicken Nutrition. I. Gross Development and Vitamin Utilization Studies Employing White Leghorn Chicks.
J. Nutrition, 41: 31, 1950.
28. Reyniers, J. A., Luckey, T. D. and Gordon, H. A.
Studies on the Growth Effect of Antibiotics in Germ-free Animals. A colloquium held at Univ. Notre Dame, June 4, 1952.
29. Johansson, K. R., Peterson, G. E. and Dick, E. C.
Effects of Dietary Aureomycin upon the Intestinal Microflora and the Intestinal Synthesis of Vitamin B₁₂ in the Rat.
J. Nutrition, 49: 135, 1953.
30. Johansson, K. R.
Response to and Assay of Vitamin B₁₂ by a Mutant of Escherichia coli.
Proc. Soc. Exptl. Biol. Med., 83: 448, 1953.
31. Peterson, G. E., Dick, E. C., and Johansson, K. R.
Influence of Dietary Aureomycin and Carbohydrate on Growth, Intestinal Microflora and Vitamin B₁₂ Synthesis of the Rat.
J. Nutrition, 51: 171, 1953
32. McInykowycz, J.
A Study on Amine Formation by Intestinal Bacteria of the Rat and the Influence of Chlortetracycline Thereon.
Thesis for the M. S. degree, University of Minnesota, 1953.
33. Bremner, J. M. and Kenten, R. H.
Paper Chromatography of Amines.
Biochem. J., 49: 651, 1951.
34. Chow, B. F., Davis, R. L. and Davis, S.
The Effect of Antibiotics and the Composition of Diets on Fecal Vitamin B₁₂ and Biotin.
J. Nutrition, 49: 657, 1953.
35. Lewis, J. J., Tappan, D. V. and Elvehjem, C. A.
Properties and Distribution of Vitamin B₁₂f.
J. Biol. Chem., 199: 517, 1952.
36. Meakins, J. and Harrington, C. R.
The Relation of Histamine to Intestinal Intoxication. II. The Absorption of Histamine from the Intestine.
J. Pharm. Exptl. Ther., 20: 45, 1923.
37. Koessler, K. K. and Hanke, M. T.
Studies on Proteinogenous Amines. XXI. The Intestinal Absorption and Detoxication of Histamine in the Mammalian Organism.
J. Biol. Chem., 59: 889, 1924.
38. Zeller, E. A.
Über den enzymatischen Abbau von Histamin und Diaminen.
2. Mitteilung. Helv. Chim. Acta., 21: 880, 1938.
39. Blashko, H., Richter, D. and Schlossman, H.
The Oxidation of Adrenaline and Other Amines.
Biochem. J., 31: 218, 1937.
40. Zeller, E. A., Stern, R. and Wenk, M.
Über die Diamin-Diamin oxydase Reaction.
Helv. Chim. Acta., 23: 3, 1940.
41. Gale, E. F.
The Bacterial Amino Acid Decarboxylases.
Adv. Enzymol., 6: 1, 1946.

II. MEDICAL SCHOOL NEWS

Coming Events

- January 7 Phi Delta Epsilon Lecture; "Present Concepts in the Management of Intussusception;" Dr. Mark R. Ravitch, Director of Surgery, Mt. Sinai Hospital, New York City; Owre Amphitheater; 8:00 p.m.
- January 7 - 9 Continuation Course in Pediatrics for General Physicians
- January 25 - 30 Continuation Course in Neurology for General Physicians and Specialists
- January 27 J. B. Johnston Lecture; "Recent Advances in the Morphology and Significance of the Cerebral Cortex;" Dr. Andrew T. Rasmussen, Professor Emeritus of Anatomy, University of Minnesota, Museum of Natural History Auditorium; 8:00 p.m.
- February 1 - 5 Continuation Course in Child Psychiatry for General Physicians and Specialists
- February 10 - 11 Continuation Course in Cancer Detection for General Physicians
- February 11 Dedication of the Elias P. Lyon Laboratories
- February 15 - 17 Continuation Course in Fundamental Advances in Internal Medicine for Internists
- February 16 Journal-Lancet Lecture; "The Biosynthesis of Heme;" Dr. David Shemin, Columbia University, New York City; Owre Amphitheater; 8:00 p.m.
- February 18 - 20 Conference on Sterility and Fertility for General Physicians and Specialists

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Meeting of the Board of Directors of the Minnesota Medical Foundation

On Tuesday, October 27, the Board of Directors of the Minnesota Medical Foundation met at the Curtis Hotel in Minneapolis at 6:00 p.m. Dr. Reuben Berman, Chairman of the 1933 Class Memorial, outlined the factors which led to the establishment of the memorial to the class of 1933. Members of that class contributed a total of \$2,500 which was presented to Dean Diehl at the annual meeting of the Minnesota Medical Alumni Association on November 6. The money has been placed in an unrestricted scholarship fund which may be distributed as the Dean sees fit.

Dr. Harold Benjamin, President of the Minnesota Medical Alumni Association, reported on the progress of the Alumni Directory. The Treasurer's Report was given by Dr. Wesley W. Spink, and a written report on the "Bulletin of the University of Minnesota Hospitals and Minnesota Medical Foundation" by Dr. Robert B. Howard, Editor, was read.

Dr. Wangenstein pointed out that within the administrative program of the University the Hospital intern has no academic status. As a consequence of this, interns who are in financial difficulty cannot turn to University loan funds or scholarship funds. The suggestion was made that a fund be raised by the Foundation for the purpose of aiding interns who are in financial need. Dr. Wangenstein and Dr. Spink reported on the very successful Foundation Day which was held on October 1. It was pointed out that the tenure of Dr. Vernon Smith as Chairman of the Membership Committee has expired. Appointment of someone to succeed Dr. Smith was deferred until the Executive Committee has had occasion to meet and discuss this important appointment. The meeting adjourned at approximately 10:30 p.m.

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Dr. Abernathy Awarded ACP Fellowship

Dr. Robert S. Abernathy, Fellow in the Department of Medicine at the University Hospitals, has been awarded a Research Fellowship in Medicine by the American College of Physicians. The appointment is effective July 1, 1954. He will work under the preceptorship of Dr. Wesley W. Spink, Professor of Medicine, on the pathogenesis of brucellosis. Dr. Abernathy is a graduate of Duke University School of Medicine. He interned in the Department of Medicine at the University of Minnesota Hospitals, and following a year as Fellow in Medicine, he served two years in the Army in Korea. Dr. Abernathy's wife, Dr. Rosalind Abernathy, is a part-time assistant in the Department of Pediatrics at the University Hospitals.

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Publications of the Medical School Faculty

- Blumenthal, J. S.: ACTH and Cortisone in Allergy. *J. Lanc.*, 73: 455, 1953.
- Kubicek, W. G., Kottke, F. J., Laker, D. J., and Visscher, M. B.: Renal Function During Arterial Hypertension Produced by Chronic Splanchnic Nerve Stimulation in the Dog. *Am. J. Physiol.*, 174: 397, 1953.
- Michelson, H. E.: Review and Appraisal of the Present Knowledge Concerning Lupus Erythematosus. *Proc. of Institute of Medicine, Chicago*, 19: Oct. 15, 1953.
- Michelson, H. E.: The Problem of Lupus Erythematosus. *Minn. Med.*, 36: 1043, 1953.
- Myers, J. Arthur: The Minnesota Medical Profession and Tuberculosis. *Minn. Med.*, 36: 944, 1953.
- Myers, J. Arthur: Andrew T. Rasmussen. *J. Lanc.*, 73: 417, 1953.
- Peterson, G. E., Dick, E. C., and Johansson, K. R.: Influence of Dietary Aureomycin and Carbohydrate on Growth, Intestinal Microflora and Vitamin B₁₂ Synthesis of the Rat. *J. Nutrition*, 51: 171, 1953.
- Schaar, Frances E.: Bone Marrow Aspiration Sites in Infants and Children. *J. Ped.*, 43: 297, 1953.
- Schmid, Rudi, Hanson, B., and Schwartz, S.: Experimental Porphyria. I. Isolation of Uroporphyrin I from Bone Marrow of Lead Poisoned Rabbits. *Proc. Soc. Exp. Biol. Med.*, 79: 459, 1952.
- Schofield, William: Research in Clinical Psychology. *J. Clin. Psychology*, 9: 313, 1953.
- Schofield, William: An Introduction to Projective Techniques and Other Devices for Understanding the Dynamics of Human Behavior. *J. Abnormal and Soc. Psychology*, 48: Apr., 1953.
- Schwab, J. H., Watson, D. W., and Cromartie, W. J.: Further Studies on the Generalized Shwartzman Reaction Produced with Group A Streptococcal Factors. *Bact. Proc.*, Aug. 10, 1953.

** Dedication of the Elias P. Lyon Laboratories -- February 11, 1954
Dedication of the University of Minnesota Medical Center Addition and Mayo Memorial -- October 21, 1954

III.

UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
WEEKLY CALENDAR OF EVENTS

Physicians Welcome

December 14 - 19, 1953

Monday, December 14

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, Moore, and Stenstrom; Todd Amphitheater, U. H.
- 11:30 - 12:30 Physical Medicine Seminar; Heart Hospital Auditorium.
- 12:15 - Obstetrics and Gynecology Journal Club; Staff Dining Room, U. H.
- 12:30 - 1:30 Physiology Seminar 201;
- 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.
- 4:00 - 5:00 Residents Conference; Presentation of Cases from University Hospitals; Heart Hospital Theater.
- 4:30 - Infectious Disease Rounds; Sta. 43, 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 - 10:00 Tuberculosis and Chest Conference; Auditorium.
- 2:00 - 3:00 Surgery Journal Club; Classroom.

Minneapolis General Hospital

- 9:30 - Pediatric Rounds; Eldon Berglund; Newborn Nursery, Station C.
- 10:30 - 12:00 Medicine Rounds; Thomas Lowry; Sta. F.
- 11:00 - Orthopedic and Fracture Rounds; Drs. John Moe and Arthur Zierold; Sta. A.
- 11:00 - Pediatric Rounds; Erling Platou; Station K.
- 12:30 - Surgery Grand Rounds; Dr. Zierold; Sta. E.
- 1:30 - 2:30 Tuberculosis Conference; J. A. Myers; Sta. M.
- 2:00 - Pediatric Rounds; Stations I and J.

Monday, December 14 (Cont.)

Veterans Administration Hospital

1:30 - Cardiac Conference; Drs. Berman, Weisbart, and Smith; Rounds Immediately following conference.

Tuesday, December 15

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.

12:30 - 1:30 Physiology 114C -- Respiration; E. B. Brown; 129 Millard Hall.

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

3:30 - Pediatric Seminar; Subject to be announced; Margaret Pijan; Sixth Floor, U. H.

3:30 - General Physiology-Biophysics Seminar; 323 Zoology Building.

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.

5:00 - 6:00 X-ray Conference; Presentation of Cases from Ancker Hospital; Drs. Aurelius, Peterson, and Niknejad; Eustis Amphitheater, U. H.

Ancker Hospital

9:00 - 10:00 Medical X-ray Conference; Auditorium.

Minneapolis General Hospital

10:00 - Psychiatry Grand Rounds; R. W. Anderson; Sta. H.

10:00 - Pediatric Rounds; Spencer F. Brown; Stations I and J.

11:30 - 12:30 Neurology-Neurosurgery Conference; Classroom, Station M.

12:30 - 2:30 Dermatology Rounds and Clinic; Carl W. Laymon and Staff.

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

1:00 - Tumor Clinic; Drs. Eder, Coe, and Lipschultz; Classroom.

Veterans Administration Hospital

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

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

9:30 - Infectious Disease Rounds; Drs. Hall, Zinneman, and Brown.

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

10:30 - Surgery-Tumor Conference; L. J. Hay, J. Jorgens and Donn Mosser; Conference Room, Bldg. I.

1:00 - Review of Pathology, Pulmonary Tuberculosis; Conference Room, Bldg. I.

1:30 - Combined Medical-Surgical Chest Conference; Conference Room, Bldg. I.

Tuesday, December 15 (Cont.)

Veterans Administration Hospital (Cont.)

- 2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III.
- 3:00 - Psychosomatic Conference; C. K. Aldrich; Surgical Conference Room, Bldg. 43.
- 4:00 - Thoracic Surgery Problems; Conference Room, Bldg. I.

Wednesday, December 16

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 Conference; Neurology Case; O. H. Wangenstten, C. J. Watson, and Staffs; Todd Amphitheater, U. H.
- 12:30 - 1:30 Physiology 114B -- Transport Seminar; Nathan Lifson and M. B. Visscher; 214 Millard Hall.
- 1:00 - 2:00 Dermatology Clinical Seminar; 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; J. D. Krafchuk; 3rd Floor Conference Room, Heart Hospital.
- 4:00 - Medicine-Physiology Cardiovascular Conference; Medicine and Physiology Staffs; Heart Hospital Theater.
- 4:30 - 5:50 Dermatology Infectious Disease Seminar; J. D. Krafchuk; 3rd Floor Conference Room, Heart Hospital.
- 5:00 - 6:00 Residents Lecture; Pelvimetry; Irwin Kaiser; Todd Amphitheater, U. H.
- 5:00 - 5:50 Urology-Pathological Conference; C. D. Creevy and Staff; Eustis Amphitheater, U. H.
- 5:30 - 7:30 Dermatology Journal Club and Discussion Group; Hospital Dining Room.
- 7:30 - 9:30 Dermatology Pathology Seminar; Review of Interesting Slides of the Week; Robert W. Goltz; Todd Amphitheater, U. H.

Ancker Hospital

- 8:30 - 9:30 Clinico-Pathological Conference; Auditorium.
- 12:30 - 1:30 Medical Journal Club; Library.

Minneapolis General Hospital

- 9:30 - Pediatric Rounds; Max Seham; Stations I and J.
- 10:30 - 12:00 Medicine Rounds; Thomas Lowry and Staff; Station D.
- 11:00 - Pediatric Seminar; Arnold Anderson; Classroom, Station I.
- 11:00 - Pediatric Rounds; Erling S. Platou; Station K.

Wednesday, December 16 (Cont.)

Minneapolis General Hospital (Cont.)

- 12:00 - Surgery-Physiology Conference; Arthur Zierold and E. B. Brown; Classroom.
12:15 - Pediatric Staff Meeting; Classroom, Station I.
1:30 - Visiting Pediatric Staff Case Presentation; Classroom, Station I.

Veterans Administration Hospital

- 8:30 - 10:00 Orthopedic X-ray Conference; E. T. Evans and Staff; Conference Room; Bldg. I.
8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker.
9:00 - Gastro-Intestinal Rounds; Drs. Wilson, Zieve, Hay, Brakel and Nesbitt.
12:30 - X-ray Conference; J. Jorgens; Conference Room, Bldg. I.
1:30 - 2:30 Infectious Disease Conference; Wesley W. Spink; Conference Room, Bldg. I.
2:30 - 4:30 Infectious Disease Rounds; Main Conference Room, Bldg. I.
5:00 - Medical Journal Club; Conference Room, Bldg. I.
7:00 p.m. Lectures in Basic Science of Orthopedics; Conference Room, Bldg. I.

Thursday, December 17

Medical School and University Hospitals

- 9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.
11:00 - 12:00 Cancer Clinic; K. Stenstrom, A. Kremen and B. Zimmermann; Todd Amphitheater, U. H.
1:30 - 4:00 Cardiology X-ray Conference; Heart Hospital Theatre.
5:00 - 6:00 Radiology Seminar; Presentation of Cases from Miller Hospital; Dr. Peterson, et al; Eustis Amphitheater, 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.

Ancker Hospital

- 8:00 - 10:00 Medical Grand Rounds; Auditorium.

Minneapolis General Hospital

- 9:30 - Neurology Rounds; Heinz Bruhl; Station I.
10:00 - Pediatric Rounds; Spencer F. Brown; Station K.
10:00 - Psychiatry Grand Rounds; J. C. Michael and Staff; Sta. 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.

Thursday, December 17 (Cont.)

Minneapolis General Hospital (Cont.)

- 1:00 - Fracture - X-ray Conference; Drs. Zierold and Moe; Classroom.
- 1:00 - House Staff Conference; Station I.

Veterans Administration Hospital

- 8:00 - Surgery Grand Rounds; Conference Room, Bldg. I.
- 8:00 - Surgery Ward Rounds; Lyle Hay and Staff; Ward 11.
- 11:00 - Surgery-Roentgen Conference; J. Jorgens; Conference Room, Bldg. I.
- 1:00 - 3:00 Metabolic Disease Conference; Drs. Flink, Heller and Hoseth.

Friday, December 18

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; Out-Patient Department, Heart Hospital.
- 11:45 - 12:50 University of Minnesota Hospitals Staff Meeting; Hospitals Report -- 1952-53; Ray Amberg; Powell Hall Amphitheater.
- 1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.
- 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; Skin Clinic; W-312, U. H.
- 2:30 - 4:00 Dermatology Hospital Rounds; H. E. Michelson and Staff; Begin at Dermatology Histopathology Room, M-434, U. H.
- 3:00 - 4:00 Neuropathological Conference; F. Tichy; Todd Amphitheater, U. H.
- 4:00 - 5:00 124 Advanced Neurophysiology Lecture; Werner Koella and Ernst Gellhorn; 111 Owre Hall.
- 4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, 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

- 9:30 - Pediatric Rounds; Wallace Lueck; Station J.

Friday, December 18 (Cont.)

Minneapolis General Hospital (Cont.)

- 10:30 - Pediatric Surgery Conference; Oswald Wyatt; Tague Chisholm; Station I, Classroom.
- 12:00 - Surgery-Pathology Conference; Dr. Zierold, Dr. Coe; Classroom.
- 1:00 - 3:00 Clinical Medical Conference; Thomas Lowry; Classroom, Station M.
- 1:15 - Pediatric X-ray Conference; Oscar Lipschultz; Classroom, Main Bldg.
- 2:00 - Pediatric Rounds; Stations I and J.

Veterans Administration Hospital

- 10:30 - 11:20 Medicine Grand Rounds; Conference Room, Bldg. I.
- 1:00 - Pathology Slide Conference; E. T. Bell; Conference Room, Bldg. I.
- 2:00 - Clinicopathologic Conference; Conference Room, Bldg. I.

Saturday, December 19

Medical School and University Hospitals

- 7:45 - 8:50 Orthopedic X-ray Conference; W. H. Cole and Staff; M-109, U. H.
- 9:00 - 10:00 Infertility Conference; Louis L. Friedman, David I. Seibel, and Obstetrics Staff; Eustis Amphitheater, U. H.
- 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.

Minneapolis General Hospital

- 8:00 - Urology Staff Conference; T. H. Sweetser; Main Classroom.
- 9:00 - Psychiatry Grand Rounds; R. W. Anderson; Sta. H.
- 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 - 11:15 Hematology Rounds; Drs. Hagen and Fifer.
- 11:15 - 12:00 Morphology . . . Dr. Aufderheide; Conference Room.