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# Metabolic Functions of Ascorbic Acid

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# I. METABOLIC FUNCTIONS OF ASCORBIC ACID *

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Our experiments designed to elucidate the pathogenesis of megaloblastic anemia in infancy were briefly reported before the Staff of the University Hospital two years age.[1] Since then the results have been fully published.[2,3] It will be recalled that we domonstrated that monkeys fed milk diets devoid of ascorbic acid not only become deficient in ascorbic acid but also develop a megaloblastic pattern in the marrow at about the time signs of scurvy appear. Dr. Sundberg studied the hematology carefully and found the marrow picture in the experimentally induced megaloblastic anemia to be very similar to that seen in megaloblastic anemia in humans.[3] The megaloblastosis complicating ascorbic acid deficiency is unaffected by vitamin $B_{12}$ but is promptly relieved by folic acid or ascorbic acid. We concluded that ascorbic acid played some role in the metabolism of folic acid.

Naturally we have pursued the problem as to the manner in which ascorbic acid might be involved in the metabolism of folic acid and the production of megaloblastic anemia. We have also been led to seek a more fundamental understanding of the functions of ascorbic acid in metabolic processes. One of us (R.J.S.) has been particularly engaged in studying the action of ascorbic acid in the degradation of tyrosine; another (C.T.S.) has taken advantage of these scorbutic monkeys to probe into the precise role of ascorbic acid in the functions of the adrenal cortex. Representative data from each of these areas of interest will be given in this report.

## PART I

### Relation of Ascorbic Acid to the Metabolism of Folic Acid in Experimental Nutritional Megaloblastic Anemia

Although the milk which is the diet of these monkeys provides only about 2 micrograms of folic acid (PGA) daily this amount is sufficient for normal blood production if accompanied by an adequate intake of ascorbic acid. Reduction of food intake to one-tenth of that ordinarily ingested does not lead to folic acid deficiency when ascorbic acid is adequate. Anorexia and reduced intake is not the means by which ascorbic acid deficiency leads to megaloblastosis.

Table I provides data demonstrating that the fecal content (bacterial synthesis) of PGA is not reduced in the ascorbic acid deficient animals even when they have become scorbutic and megaloblastic.

The scorbutic animal absorbs PGA and the triglutamate of PGA with sufficient efficiency to enable one to cure of prevent the megaloblastosis by oral administration of these substances in small amounts. Whether the heptaglutamate of PGA can also be absorbed efficiently by the scorbutic animal is not certain.

The conjugase which liberates free PGA from its conjugates is active even in advanced scurvy. In Table II it may be seen that the same ratio of free to total PGA exists in the normal and the scorbutic monkeys livers, namely approximately 50% free. Furthermore, livers from scorbutic

* These remarks were illustrated by a number of lantern slides which it was impractical to reproduce. Some of the statements, seemingly unsupported by data, were substantiated by data shown in lantern slides.

megaloblastic monkeys contain conjugase which will liberate free PGA from its conjugate in yeast as well as does the standard hog kidney conjugase preparation, and does so without the addition of ascorbic acid.

TABLE I

AVERAGE EXCRETION OF PGA IN FECES AND URINE - MONKEYS
(Various Milk Diets)

| | FECES | | URINE | LIVER |
|---|---|---|---|---|
| | Free PGA | Total PGA | Total PGA | Total PGA |
| | (Micrograms per 24 hours) | | | (mcg/gm) |
| Ascorbic acid adequate | 6 | 29 | 0.30 | 1.10 |
| Ascorbic acid deficient | 5 | 27 | 0.18 | |
| Scorbutic | 2 | 27 | | |
| Scorbutic and megaloblastic | 6 | 32 | | 0.28 |

TABLE II

FREE VERSUS TOTAL PGA IN LIVERS
(All Types of Diets)

| | FREE PGA | TOTAL PGA | % FREE |
|---|---|---|---|
| | (micrograms per gram) | | |
| Ascorbic acid adequate (5) | .27 | .60 | 45 |
| Ascorbic acid deficient (7) | .07 | ..13 | 54 |

PGA can cure the megaloblastosis in the scorbutic monkey without the aid of ascorbic acid. Therefore the animal is presumably able to convert PGA to folinic acid (FNA). FNA itself is active in smaller quantities than PGA,[3] and ascorbic acid is not requredd for the stability or action of either of these compounds. Data on these points is provided in Table III where it is also shown that the effect of ascorbic acid may be to promote the efficiency of the conversion of PGA to FNA

It also appears that the action of ascorbic acid is quite specific, for much larger doses of closely related compounds like glucoascorbic acid do not have any effect on the megaloblastosis or the scurvy. Other members of the B complex of vitamins (indicated in Table III), not included as supplements to the diet, are apparently not implicated in the megaloblastosis of the scorbutic monkey.

TABIE III

EFFECTS OF TREATMENT OF SCORBUTIC MEGALOBIASTIC MONKEYS
(Approximately 2 Kilo in Weight, Diet 4BA)

| No. | Treatment, intramuscular | Days Rx | Scurvy | Wt. | Marrow | Max. Retic. % | Hb. | LIVER, mcgm/gm $B_{12}$ | PGA (Total) | FNA |
|---|---|---|---|---|---|---|---|---|---|---|
| | 3 Normals - Biopsy | | | | Normo | 1.6 | | 1.3 | 1.33 | .027 |
| 81 | Untreated | | Scorbutic | | Mego | (20) | | .95 | 0.17 | .010 |
| 92 | 100 micrograms PGA | 12 | No effect | - | Normo | 20 | - | 1.28 | 0.39 | .033 |
| 100 | 1 mg ascorbic acid | 18 | Healing | + | Normo | 28 | + | 1.22 | 0.61 | .020 |
| 91 | 50 mg ascorbic acid | 12 | Healing | + | Normo | 6 | 0 | .95 | 0.19 | .040 |
| 82 | 50 mg glucoascorbic acid | 18 | No effect | - | Mego | 24 | - | 1.28 | 0.13 | .005 |
| 83 | 50 mg glucoascorbic acid | 15 | No effect | - | Mego | 12 | - | 1.20 | 0.16 | .003 |
| 68 | 5 gm Brewers yeast ($PG_7A$) | 9 | No effect | - | Mego | 0.5 | 0 | 1.30 | 0.24 | .005 |
| 89 | 50 mg choline | 5 | No effect | - | Mego | 24 | - | 1.26 | 0.21 | .009 |
| 99 | 100 mg PABA<br>50 mg choline | 5<br>4 | No effect | - | Mego | 6 | | 1.13 | 0.06 | .003 |
| 85 | 10 mg biotin, 50 mg inositol<br>50 mg choline, 100 mg PABA | 7 | No effect | - | Mego | 18 | - | 1.25 | 0.24 | .003 |

Infection can cause marked depletion of the liver content of vitamin $B_{12}$ and PGA. (Table IV). Addition of PGA to the diet prevents depletion in the liver in ascorbic acid deficiency. Infection did not appear to play a major role in these experiments with ascorbic acid deficient animals. The importance of infection in the metabolism and requirements of PGA and vitamin $B_{12}$ is now under investigation in our laboratory.

TABLE IV

LIVER CONTENT $B_{12}$ AND PGA - MONKEYS
(Various Milk Diets)

| | Micrograms per gram, wet | |
|---|---|---|
| | $B_{12}$ | Total PGA |
| Controls (4) | 1.23 | 1.10 |
| Scurvy, megaloblastic (5) | 0.56 | 0.28 |
| Scurvy, megaloblastic, $B_{12}$ I.M. prophylactic (3) | 0.54 | 0.07 |
| Scurvy, normoblastic, PGA p.o. or I.M. prophylactic (4) | 0.58 | 1.43 |
| Starvation, ascorbic acid provided, normoblastic (2) | 0.63 | 0.68 |
| Sick, normoblastic, ascorbic acid provided (5) | 0.48 | 0.75 |
| Sick, megaloblastic, ascorbic acid provided (6) | 0.31 | 0.17 |

Because of the proposed relationship of ascorbic acid to function of the adrenal cortex, the action of cortisone on the megaloblastosis and scurvy was tested. 10 mg cortisone acetate (Merck) per kilogram intramuscularly daily for twelve days had no effect on megaloblastosis or scurvy in a monkey.

A list of the substances effective or ineffective in megaloblastosis of scorbutic monkeys is provided in Tables V and VI.

TABLE V

SUBSTANCES HAVING NO EFFECT ON MEGALOBLASTOSIS IN SCORBUTIC MONKEYS

| | Daily Dose | | Daily Dose |
|---|---|---|---|
| Vitamin $B_{12}$ | 15 mcgms I.M. | Glucoascorbic Acid | 50 mg I.M. |
| Choline | 50 mg I.M. | Ascorbic Acid | 100 mg } I.M. |
| Paraminobenzoic Acid | 100 mg I.M. | and "Aminopterin" | 0.2 mg } |
| Inositol | 50 mg I.M. | Aureomycin | 250 mg p.o. |
| Biotin | 10 mg I.M. | Cow's Milk Protein | 7 gms/Kilo. |
| | | Cortisone | 10 mg/Kilo. |

TABLE VI

SUBSTANCES EFFECTIVE IN MEGALOBLASTOSIS OF SCORBUTIC MONKEYS

| | Daily Dose |
|---|---|
| Folic Acid (PGA) | 100 mcgm I. M. |
| "Teropterin" (PGA triglutamate) | 2.5 mg p.o. |
| Folinic Acid (FNA) | 7.5 mcgm I. M. |
| Ascorbic Acid | 1 mg I. M. |

Thus we have indicated a number of means by which ascorbic acid might play a role in the metabolism of folic acid. We have shown that none of these has been demonstrated to be tenable as a satisfactory explanation. At present we are most concerned with the efficiency of intestinal absorption of the naturally occurring heptaglutamate of folic acid in the scorbutic monkey. This is important because the animal receives its supply of folic acid naturally in the form of the heptaglutamate whether obtained from the diet or the intestinal bacterial synthesis.

PART II

The Role of Ascorbic Acid in the Metabolic Degradation of Tyrosine

The fact that ascorbic acid plays an important role in the metabolism of tyrosine has been demonstrated by Levine et. al.[4-8] and Govan and Gordon[9] in premature infants, by Sealock et. al.,[10-16] Woodruff et. al.,[17] Painter and Zilva[18] in guinea pigs, and by Rogers and Gardner[19] in human adults. Deficiency of ascorbic acid resulted in an increased excretion in the urine of "tyrosyl compounds" (p-hydroxy-phenyl-pyruvic acid, p-hydroxyphenyllactic acid and tyrosine). Swendseid et. al.[20,21] reported an increased excretion of the p-hydroxyphenyl acids in the urine occurred in pernicious anemia patients in relapse and that it returned to normal when liver therapy was given. One patient in their series who was scrobutic failed to show this increased excretion of phenoloc acids until the ascorbic acid deficiency was corrected. The experience of Dyke et. al.[22] with three ascorbic acid deficient pernicious anemia patients who had become refractory to liver therapy, but who had responded normally to liver therapy once the ascorbic acid deficiency had been corrected, would suggest that this vitamin has some role in the functioning of the anti-pernicious anemia factor.

It was these reports which prompted the study of these metabolites of tyrosine in the scorbutic and megaloblastic monkey. It was first demonstrated[23] that neither in the scorbutic nor in the megaloblastic monkey is there a spontaneous tyrosyluria. TABLE VII

TABLE VII

URINARY EXCRETION OF P-HYDROXYPHENYL COMPOUNDS BY MONKEYS *

| | Number of Determinations | Average Excretion mg/kilo/24 hours |
|---|---|---|
| Controls (Ascorbic acid adequate) | 44 | 13.5 |
| Scrobutic | 38 | 12.2 |
| Scorbutic and megaloblastic | 15 | 13.7 |

*Compiled from data in a previous report of Salmon and May[23]

If, however, the monkeys were given a load of l-tyrosine corresponding to 2 gm/kilo body weight, while in the normal 10-13% of the load was excreted in the urine as tyrosyl compounds, in the scorbutic animal 30-100% of the load was thus excreted depending upon the severity of ascorbic acid deficiency. This tyrosyluria was quickly abolished by giving ascorbic acid.

Rodney et. al.[24,25] demonstrated that liver slices from pteroylglutamic acid (PGA) deficient rats failed to oxidize tyrosine at the normal rate and that the addition of PGA restored the oxidation to some extent. Ascorbic acid, however, had no effect. Woodruff et. al.[17] showed that PGA would abolish the tyrosyluria of scorbutic guinea pigs. It was demonstrated[23] that in a scorbutic monkey PGA even at a level of 95 mg per day (both intramuscularly and orally) was unable to modify the tyrosyluria

Table VIII

TABLE VIII

URINARY EXCRETION OF P-HYDROXYPHENYL COMPOUNDS BY MONKEYS LOADED WITH L-TYROSINE (2 gm/kilo)

| Monkey No. | Condition | % of Load Excreted |
|---|---|---|
| 7 | Control (Ascorbic acid adequate) | 13.3 |
| 24 | Scorbutic | 31.4 |
| 14 | Scorbutic, treated with PGA, 5 mg daily | 58.5 |
| 24 | Scorbutic and megaloblastic, treated with PGA, 95 mg daily | 73.2 |
| 15 | Scorbutic, megalobaastic, treated with "Aminopterin", .2 mg and ascorbic acid, 100 mg | 19.6 |

* Compiled from data in a paper by Salmon and May[23]

That ascorbic acid is more specific than PGA in preventing tyrosyluria is shown by the work of Govan and Gordon[9] in which only four out of ten premature infants responded to PGA therapy, whereas five of six who were refractory to PGA subsequently responded to ascrobic acid administration. Morris et. al.[26] have recorded a similar experience. Rienits[27] using an extract of scorbutic guinea pig liver showed that ascorbic acid restored the power of such an extract to oxidize tyrosine, almost to that of a similar extract prepared from the liver of a normal animal. Iso-ascorbic acid and d-gluco-ascorbic acid both failed to do this. Further evidence that ascorbic acid acts independently of PGA was that ascorbic acid reduced tyrosyluria almost to normal in a scorbutic monkey in whom PGA had been blocked by Aminopterin.[23]

Effect of Folinic Acid (Citrovorum Factor)

Nichol and Welch[28] found that the amount of citrovorum factor (folinic acid) which could be demonstrated after the incubation of liver slices with PGA was greatly enhanced by the presence of ascorbic acid.

It was thought that the failure of the PGA to prevent tyrosyluria in the monkey might have been due to the failure to accumulate folinic acid in the face of severe scurvy. It was demonstrated[29] that folinic acid will not prevent the tyrosyluria produced by loading a scorbutic monkey with l-tyrosine. In another attempt 1 mg of folinic acid per day for four days only reduced the excretion of the tyrosine as tyrosyl compounds by a few percent whereas ascorbic acid given subsequchtly reduced it to normal promptly.

TABLE IX

EFFECT OF CORTICOTROPIN, CORTISONE AND FOLINIC ACID ON URINARY EXCRETION OF P-HYDROXYPHENYL COMPOUND

| Monkey No. | Day of Loading With L-Tyrosine (2 gm/Kilo) | | Average Excretion in 24 hours |
|---|---|---|---|
| 108 | 1 - 2 | No ascorbic acid for 40 days | 27% of load |
| | 4 - 8 | Corticotropin, 10-20 mg/Kilo per 12 hrs. I.V. | 58% of load |
| | 9 - 14 | Cortisone, 10-15 mg/Kilo per 12 hrs. I.M. | 60% of load |
| | 15 - 18 | Folinic acid, 2 mg daily I.M. | 49% of load |
| | 19 - 22 | Ascorbic acid, 40 mg/Kilo daily I.M. | 17% of load |

Effect of Cortisone and Corticotropin

Severe scurvy might have interfered with the functioning of the adrenal hormones. This seemed to be the case when it was found[29] that scorbutic monkeys treated with cortisone before and during loading with tyrosine failed to develop tyrosyluria more than that of a normal. This would agree with the work of Ferrero[30] on suprarenal insufficiency. However, in a subsequent experiment in which a tyrosyluria was established prior to the administration of cortisone the latter failed to abolish it. This agrees with the experience of Levine et. al.[31] who found cortisone effective in three, but ineffective in two cases of induced tyrosyluria in premature infants. Contrary to the experience of these workers, two attempts to cause abolition of tyrosyluria in the scorbutic monkey by injection of Corticotropin failed. Tables IX and XI.

Effect of Complete Adrenalectomy

If ascorbic acid deficiency causes tyrosyluria by failure of the adrenal glands, then complete removal of those glands should cause a pronounced tyrosyluria even in the presence of ascorbic acid. Bilateral adrenalectomy was performed in a healthy monkey who had been proved to react normally to a tyrosyl loading test. Loading tests were again performed ten days and two months later. In the first test there was actually less tyrosyluria than before the adrenalectomy while in the second test it was still within the limits of normal. Table X

TABLE X

EFFECT OF ADRENALECTOMY ON EXCRETION OF P-HYDROXYPHENYL COMPOUNDS BY A MONKEY

| Monkey No. | | % of Load Excreted |
|---|---|---|
| 52 | Loading test before adrenalectomy | 9.7 |
| | Loading test 10 days after operation | 3.6 |
| | Loading test 2 monts later | 14.1 |

Effect of Sulfhydryl Groups

It has been claimed that ascorbic acid activates enzymes which depend on the presence of sulfhydryl groups for their activity. Whether it functions in the prevention of tyrosyluria by its stabilizing effect on sulfhydryl groups in some enzyme system might be tested in two ways: either by administration of excess of reduced sulfhydryl groups to a scorbutic animal and testing its power to prevent a tyrosyluria, or by giving an inhibitor of sulfhydryl enzymes to a normal animal and testing whether a tyrosyluria would develop on loading with tyrosine.

An attempt was made by giving 50 mg of reduced glutathione per kilo body weight, thrice daily, to a scorbutic monkey in whom corticotropin had already failed to abolish tyrosyluria produced by loading with l-tyrosine. Table XI shows there was some lowering of the tyrosyluria. Another animal which was severely scorbutic, but had not previously been subjected to corticotropin therapy, was injected intramuscularly with 200 mg of reduced glutathione per kilo twice daily for three days before loading with tyrosine was commenced and continued during the later procedure. The excretion of tyrosyl compounds remained within normal limits, 13.9% of load. Both these animals showed severe toxic symptoms and ultimately died. Another ascorbic deficient but not scorbutic monkey was loaded with l-tyrosine and 200 mg of reduced glutathione per kilo injected twice daily, beginning the second day of loading. This was continued for five days when toxic symptoms began to appear and it was stopped. The excretion of tyrosyl compounds rose to 29% of the load on the third day but then fell gradually to 15.4% on the sixth day when treatment was discontinued. (Table XII)

TABLE XI

URINARY EXCRETION OF P-HYDROXYPHENYL COMPOUNDS BY MONKEYS LOADED WITH L-TYROSINE (2 gm/kilo)

| Monkey No. | Day of Loading | | % Excreted |
|---|---|---|---|
| 78 | 1 - 2 | Scorbutic | 35.2 |
| | 3 - 6 | 10 mg corticotropin I.M., t.i.d. | 56.0 |
| | 7 - 9 | No treatment | 49.0 |
| | 10 - 12 | Glutathione, 50 mg/kilo t.i.d., I.M. | 33.0 |

Table XII seems to suggest that reduced glutathione may be able to reduce the tyrosyluria, but the toxic effects of the drug make the results equivocal.

Another ascorbic acid deficient monkey was loaded with l-tyrosine and then given injections of B.A.L. (British anti-lewisite or 2,3 dithiopropanol) while loading was continued. At first 10 mg per kilo was given intramuscularly twice daily, but produced vomiting. The dose was then changed to 5 mg per kilo four times a day which still caused some vomiting. When the dose was reduced to 5 mg per kilo thrice daily vomiting ceased. The average excretion of tyrosyl compounds during the period when toxic symptoms were shown was 13% but at the lower dosage it rose to 34.5%. Again it would appear that the sulfhydryl compound might have some effect in re-

TABLE XII

URINARY EXCRETION OF P-HYDROXYPHENYL COMPOUNDS BY MONKEY LOADED WITH L-TYROSINE (2 gm/kilo) AND TREATED WITH SULPHYLDRYL COMPOUNDS

| Monkey No. | Day of Loading | | Average Excretion (%) |
|---|---|---|---|
| 110 | | Scorbutic, treated with glutathione 200 mg/kilo b.i.d., I.M. | 13.9 |
| 116 | 1 | Ascorbic deficient but not scorbutic | 11.2 |
| | 2 | Ascorbic deficient but not scorbutic | 19.8 |
| | 3 | Glutathione 200 mg/kilo b.i.d., I. M. | 29.4 |
| | 4 | Glutathione 200 mg/kilo b.i.d., I.M. | 20.8 |
| | 5 | Glutathione 200 mg/kilo b.i.d., I.M. | 18.3 |
| | 6 | Glutathione 200 mg/kilo b.i.d., I.M. | 15.4 |
| 117 | 1 - 2 | Ascorbic deficient | 24.5 |
| | 3 - 6 | BAL 20 mg/kilo/day | 13.0 |
| | 7 - 11 | BAL 15 mg/kilo/day | 34.5 |

ducing the tyrosyluria but the results were rendered equivocal by the toxicity of the drug.

A strong healthy monkey well supplied with ascorbic acid was loaded with tyrosine and given intramuscular injections of sodium iodoacetate: 20 mg per kilo body weight once a day for four days, and then 20 mg per kilo twice a day for four days. At that point hematuria developed and the animal died the following day. Even though the dosage was persisted in until death occurred no tyrosyluria developed; the average excretion without iodoacetic being 5.6% and during injection of that drug only 7.0% of the tyrosine load.

There is some indication that sulfhydryl compounds might be effective in preventing tyrosyluria if a suitable dosage which could be tolerated for a sufficient time could be found. Barron and Singer[32] have pointed out that inhibition experiments with sulfhydryl enzymes must be done with several different inhibitors so that the failure of iodoacetate to produce tyrosyluria in the tyrosine-loaded animal does not prove that a sulfhydryl enzyme is definitely not involved. Further experiments with other inhibitors must be tried. Table XIII gives a summary of the information so far gained concerning the mechanism of action of ascorbic acid in preventing tyrosyluria in an animal loaded with l-tyrosine.

TABLE XIII

URINARY EXCRETION OF P-HYDROXYPHENYL COMPOUNDS
BY MONKEYS LOADED WITH L-TYROSINE

Increased when ascorbic acid is deficient

Unaffected by Vitamin $B_{12}$
Folic Acid
Folinic Acid
Corticotropin

Cortisone has a variable effect.
Possibly reduced by sulfhydryl compounds at toxic levels.
Reduced to normal by ascorbic acid even if Aminopterin given.

Normal when ascorbic acid is adequate

Unaffected by complete adrenalectomy.

It seems clear that ascorbic acid does not function through the adrenal gland since there is no tyrosyluria when that gland is entirely removed. Any effect produced by adrenal hormones must be due to their action on some other system, which cannot be brought into action by those hormones alone. Again the mechanism by which PGA can abolish tyrosyluria appears to be distinct from that by which ascorbic acid operates; since the latter does so even when the former is blocked by Aminopterin. Even if ascorbic acid increases the availability of folinic acid produced from PGA, which might explain the effect of ascorbic acid in megaloblastosis, this mechanism does not explain its effect on tyrosyluria as folinic acid itself is impotent in this respect. A more fundamental role of ascorbic acid might be in maintaining the integrity of sulfhydryl enzymes involved in the various steps of tyrosine metabolism. Attempts to gain information concerning this possibility by the use of sulfhydryl compounds or their inhibitors have resulted so far in only equivocal results. Experiments along these lines are being continued.

PART III

Adrenal Cortical Function in Scurvy

INTRODUCTION

Since the isolation of ascorbic acid in high concentration from the adrenal cortex,[33] interest has been directed toward the precise role of this vitamin in the function of the adrenal cortex. Depletion of adrenal ascorbic acid follows stimulation of the gland by corticotropin or a variety of non-specific stresses in the rat, mouse and guinea pig,[34-41] but not the chick:[42] cholesterol, also present in high concentration in the adrenal cortex, is similarly labile.[34] It has been proposed that cholesterol is the precursor of the steroid hormones and this has been supported by the chemical similarities[43] and the demonstration of tagged pregnanediol in the urine of women ingesting tagged cholesterol.[44] In an unconfirmed report, the isolation of a compound suggesting an ascorbic acid-corticoid conjugate has been claimed.[45] From these observations it might be inferred that the role of ascorbic acid in the adrenal cortex is to combine with hormone precursors to form the active hormone. Alternative hypotheses are that ascorbic acid has an equally significant role in the facilitation of enzyme systems involved in the synthesis and release of adrenocortical hormones, or that the observed fluctuations are coincidental.

Data obtained in attempts to clarify this issue have been contradictory. Giroud and co-workers, employing a bioassay for adrenal cortical hormones developed in their laboratory and not in widespread usage, have reported a decrease in adrenal hormones in the urine of ascorbic acid deficient humans and a return to normal during the administration of ascorbic acid.[46-50] The urinary excretion of 11-oxysteroids and 17-ketosteroids, as determined by chemical methods, has been reported as normal in adult patients with gross scurvy.[51,52] In the dog, no correlation was found between the ascorbic acid and adreocortical hormone content of adrenal venous blood.[53]

Rats pretreated with ascorbic acid fail to develop an eosinopenia after the administration of epinephrine.[54] An eosinopenia has been noted in the scorbutic guinea pig.[55] The four hour eosinophil response after the administration of corticotropin has been reported as normal in adult patients with scurvy and in one of these patients there was a normal rise in the urinary 17-ketosteroids after 48 hours of corticotropin therapy.[52] In the ascorbic acid deficient guinea pig, at a time when the adrenocortical ascorbic acid is extremely low, a single injection of corticotropin is followed by a depletion of adrenal cholesterol, a lymphopenia, and an eosinopenia.[40,55]

Large amounts of ascorbic acid prevent adrenal hypertrophy and prolong survival in rats and guinea pigs exposed to cold.[56] There is no fall in adrenocortical cholesterol and ascorbic acid after stress (other than corticotropin) in animals pretreated with corticoids.[57,58] A decrease in the urinary excretion of ascorbic acid has been reported in humans after surgical procedures, burns, and fractures, periods when increased adrenal activity might be expected.[59,60,61]

In the scorbutic guinea pig hypertrophy of the adrenal gland has been reported[62,63] as well as an initial increase followed by a late decrease in adrenal cholesterol.[64] The administration of adrenocortical hormones to the guinea pig on an ascorbic acid free diet has been reported to retard the onset of scurvy and prolong life.[65,66,67] It has been reported that corticotropin and cortisone do not alter the poor wound healing and have a questionable effect on the hemorrhagic manifestations in the scorbutic guinea pig.[55,66,67]

## PLAN OF EXPERIMENTS

An effort to determine the effect of ascorbic acid deficiency on adrenal function was made in the scorbutic monkey utilizing standard tests of adrenal function. The elimination of ascorbic acid from the diet given these animals also results in folic acid (PGA) deficiency, which is evidenced by the development of a megaloblastic bone marrow.[3] When the adrenal function tests had been applied in these deficiency states, specific forms of therapy were instituted, and their effect on the adrenal function tests evaluated.

The function tests selected were intravenous insulin tolerance test, serial fasting eosinophil counts, and the four hour eosinophil response to corticotropin.

The immature rhesus monkey is especially suited for such a study. This species is unable to synthesize ascorbic acid, exhibits many anatomical and functional similarities to the human, and, under the conditions of the experiments, has a low incidence of morbidity due to natural causes. Elimination of the metabolic fluctuations associated with sexual maturity was insured by the use of immature monkeys.

The monkeys were housed in individual metabolism cages, in a well ventilated room kept at relatively constant temperature. The basic diet consisted of a mixture of powdered cows milk and water, closely resembling whole milk in its nutritional content. After the addition of copper sulfate, all milk was boiled for five minutes to remove the ascorbic acid. All monkeys received as dietary supplements vitamins A and D, crystalline vitamin $B_{12}$, B complex vitamins other

than folic acid, and iron. A more detailed account of the nutritional aspects of the animals appears in a previous publication from this laboratory.[3]

Control animals received 50 milligrams of crystalline ascorbic acid by mouth daily and thrived. Monkeys deprived of ascorbic acid were vigorous and gained well for the first 30-40 days. A plateau in growth then occurred, which was followed, in the next 10-20 days, by anorexia, progressive weight loss, roughening of the coat, and a decrease in general activity. The joints became swollen and tender. Periorbital hemmorrhages heralded gross scurvy and even before this sign was noted characteristic X-ray changes were present in the long bone. A megaloblastic bone marrow was usually noted within 2 weeks after the animal became scorbutic.

Adrenal function tests were completed in these animals and then the effects of therapy were determined. One scorbutic animal was treated with ascorbic acid and another with folic acid. Preformed folinic acid was administered to a scorbutic, megaloblastic animal, as data has been reported indicating that ascorbic acid increased conversion of folic acid to folinic acid by the livers of rats.[68]

In an effort to define the role of ascorbic acid separately from folinic acid, Aminopterin* was used in one monkey to block the action of folinic acid. The effect of reduced glutathione was determined in a scorbutic monkey because of 1) possible interrelations between adrenal steroids and sulfhydryl compounds,[69] 2) the fact that many enzyems are inactive unless sulfhydryl groups are available,[70] and 3) the possibility that as ascorbic acid serves to keep glutathione in the reduced state.[71] Cortisone was administered to a scorbutic, megaloblastic animal in order to observe its effects on the adrenal function tests, the symptoms, and the histological lesions in scurvy.

As inanition is a constant feature of scurvy, a wasted animal suffering from dysentary was subjected to the adrenal function tests to serve as a "sick control."

After serving as a control, one monkey was subjected to a bilateral total adrenalectomy, in order that the responses to the adrenal function tests could be observed in the certain absence of adrenal hormones. After the immediate post-operative period, this animal was maintained in good condition by adding a $NaCl$-$NaHCO_3$ mixture to its diet. 50 milligrams of ascorbic acid was continued orally each day. The animal was without his adrenal medullary tissue as the result of surgery, so it became necessary to define the role of epinephrine in carbohydrate homeostasis under the existing experimental conditions. An epinephrine tolerance test was performed in one ascorbic acid deficient animal, and an insulin-epinephrine tolerance test was carried out in the adrenalectomized and in another ascorbic-acid-deficient monkey.

## METHODS AND TERMINOLOGY

The intravenous insulin tolerance test described by Albright was utilized.[72] A normal response was considered to include a 50-60% depression of blood sugar during the first half hour of the test and a return to fasting level by 2 hours.

In the epinephrine tolerance test 0.15 of a cc. per kilogram of 1:1000 Adrenalin was administered subcutaneously. In the combined epinephrine-insulin tolerance test this same dose of Adrenalin was given simultaneously with the insulin in an I.V. insulin tolerance test. The eosinophil counts were done according to the method of Randolph[73]. The 4-hour corticotropin test was that described by Thorn.[74]

Control animals received 50 milligrams of crystalline ascorbic acid daily. An animal designated as "ascorbic acid deficient" was one which had not received ascorbic acid for 30 days or more, and exhibited none of the gross clinical

* Supplied by the Lederle Laboratories

signs of scurvy. An animal was considered scorbutic when characteristic X-ray changes were present in the wrists, periorbital hemmorrhages had appeared, and the bone marrow was still normoblastic. When a megaloblastic bone marrow was noted, the animal was considered to be scorbutic and folic acid deficient.

The folinic acid utilized in these experiments was synthesized at the Eli Lilly laboratories and supplied to us through the courtesy of Dr. Edward Campbell. We are grateful to Dr. Edwin E. Hays, Director of Research, Armour and Company for the adrenocorticotrophic hormone used in these experiments.

## RESULTS

### Insulin Tolerance Tests

The results are tabulated in Table I. In three control animals (#33, 52, 118) receiving intravenous insulin tolerance tests, there occurred the expected initial depression in blood sugar, with the maximal depression occurring between 30-90 minutes. In two of these monkeys (#52, 118) a return to the fasting level occurred. In #33 the fasting blood sugar was somewhat higher than usual, possibly as a result of the excitement induced in handling the animal at the commencement of the test. This might explain the apparent failure in recovery.

The insulin tolerance curve in the "sick control" (#134) was similar to that seen in the controls, although blood sugar levels tended to be elevated throughout the test period and insulin depression of the blood sugar was less marked.

Monkey #52, twenty-five days after adrenalectomy, reacted as expected to the administration of insulin. The depression of the blood sugar was marked and no recovery phase was apparent at the end of 2 hours; the test was terminated at this time because of generalized twitching which responded to intravenous glucose.

Of the three ascorbic acid deficient animals subjected to insulin tolerance tests, one (#122) had a relatively normal curve. Another monkey (#121) had an initial hyperglycemia, followed by a normal depression of blood sugar in the second phase, and adequate recovery. The third animal (#109) exhibited a distinctly abnormal curve. There was an initial hyperglycemia, only moderate depression of the blood sugar during the second phase, and a hyperglycemia at the end of 2 hours.

When the grossly scorbutic animals (#106, 113) were administered insulin, abnormal curves were again noted. #106 had a curve similar to that seen in #109, the ascorbic-acid-deficient animal, an initial hyperglycemia, no depression of the blood sugar during the second phase and a hyperglycemic level at 2 hours. #113 had a marked elevation of the fasting blood sugar, and there was a gradual irregular fall throughout the test to a relatively normal level.

The intravenous insulin tolerance tests in the scorbutic and folic acid-deficient monkeys (#107, 113) were also abnormal in the same fashion; an initial hyperglycemia, little lowering of the blood sugar during the second phase, and hyperglycemia at 2 hours was noted.

Thus in five of the seven monkeys deficient in ascorbic acid an abnormal response to insulin was encountered rather consistently. It was characterized by an initial hyperglycemia, insulin unresponsiveness during the second phase, and a tendency toward hyperglycemia levels at two hours.

Five days after the administration of small doses of ascorbic acid in #105, a scorbutic animal, the insulin tolerance curve was typically abnormal. Repetition of the insulin tolerance test at the end of 25 days of therapy revealed a normal curve.

A typically abnormal curve was obtained in #111, a scorbutic animal, which had been treated with glutathione.

The treatment of #113, scorbutic and folic acid deficient, with folinic acid did not alter the initial hyperglycemia, but there was a return of normal insulin responsiveness during the second phase. The two-hour level was considerably lower than the fasting blood sugar.

In the scorbutic monkey treated with Aminopterin (#111) and the scorbutic and folic acid-deficient animal treated with cortisone (#107) the insulin tolerance tests were normal.

The administration of epinephrine to #119, an ascorbic acid deficient monkey, and the simultaneous administration of epinephrine and insulin to #125, ascorbic-acid-deficient, and #52, adrenalectomized, resulted in abnormal curves similar to those described for the insulin response in the ascorbic acid deficient animals.

Eosinophils

The results of the serial eosinophil counts were also intriguing. A progressive and marked eosinopenia, lowest in the scorbutic and folic-acid-deficient monkeys was noted. The adrenalectomized monkey had a marked eosinopenia immediately after surgery, which persisted for 2 months.

While eosinopenia was still marked, during the third month a slight increase was observed. Obviously the low eosinophil counts in some of the scorbutic and folic-acid-deficient animals made testing the response to corticotropin impossible. Whenever the eosinophil count was elevated, the customary depression in the four-hour corticotropin test occurred in the control, ascorbic acid-deficient, and scorbutic monkeys.

The administration of ascorbic acid to two scorbutic monkeys (#12, 105) was followed by a return of the eosinophil count to normal. The speed of recovery appeared to be proportional to the level of dosage. Folic acid, administered to a scorbutic (#12) and a scorbutic and folic-acid-deficient animal (#24) failed to influence the eosinophil count. Folinic acid was similarly ineffective, when given to a scorbutic and folic acid deficient monkey (#113). These results appear in Table XV.

Although microscopic changes were present in the bones of the scorbutic and folic-acid-deficient animal (#107), treated with cortisone, they were not characteristic of healing scurvy.

DISCUSSION

Consideration of the data obtained utilizing the eosinophil count as a measure of adrenal cortical function leads to certain practical conclusions. It is clear that in the monkey substances other than the adrenocortical hormones can produce an eosinopenia in the peripheral blood, as the adrenalectomized animal had a marked depression of eosinophils. This suggests that the adrenal cortical hormones may act by facilitating the action of substances more intimately involved in the control of the level of circulating eosinophils. It is probably not the deficiency of ascorbic acid itself which directly leads to the eosinopenia of scurvy, as the adrenalectomized animal had normal plasma levels of ascorbic acid. It is possible that ascorbic acid opposes the action of those mechanisms producing a reduction in eosinophils. From these observations it might be inferred that a depression of eosinophils is at times totally unrelated to adrenal cortical activity.

Although the total number of insulin tolerance tests is admittedly small, certain relationships seem worthy of comment. It is apparent that the abnormal response to insulin in the scorbutic animals was entirely different from that observed in the adrenalectomized monkey. Furthermore, the adrealectomized animal responded like the scorbutic animals when epinephrine was administered simultaneous to insulin injection. The administration of cortisone to the acorbutic folic-acid-deficient monkey resulted in a normal repsonse to insulin. From these observations certain hypotheses might be formulated. The abnormal

response to insulin in the scorbutic monkeys might be due to an increase in the activity of epinephrine. This might result from an actual increase in the production of epinephrine or a decrease in substances affecting the degradation of opposing the action of epinephrine. If cortisone opposes the action of epinephrine and does not require ascorbic acid for full activity, it might be assumed that the scorbutic animals were deficient in adrenal cortical hormones. If cortisone does require adequate ascorbic acid for activity, a physiological deficiency could be postulated in scurvy. This might be overcome by the administration of larger amounts of the hormone, thus restoring any epinephrine opposing action of cortisone. The activity of hepatic phosphorylase might be the focal area for such interactions, as epinephrine has been reported to affect the activity of this enzyme.[75] It would appear that the insulin tolerance test is not a definitive measure of adrenal cortical function in the scorbutic monkey.

This matter may be resolved by additional data we are collecting: 1) the determination of the response to insulin in scorbutic animals with the action of epinephrine opposed by ergotoxine, 2) insulin tolerance tests in cortisone treated adrenalectomized animals, 3) Epinephrine tolerance tests in control and adrenalectomized monkeys, and 4) Epinephrine-insulin tolerance tests in control and cortisone-treated scorbutic animals.

It becomes increasingly obvious that it will be necessary to measure the urinary excretion of adrenal cortical hormones in scurvy to ascertain the role of ascorbic acid in adrenal function.

BIBLIOGRAPHIES


1. Experimental Prodcction of Megaloblastic Anemia in Relation to Megaloblastic Anemia in Infants.
Charles D. May, M. D.; Edward N. Nelson, M. D.; Robert J. Salmon, M. Sc.; Charles U. Lowe, M. D.; Roger I. Lineke, M. D. and R. Dorothy Sundberg, Ph D.
Bull. Univ. Minn. Hosp. 21: 208,1950.

2. Pathogenesis of Megaloblastic Anemia in Infancy
Charles D. May, M. D.; E. N. Nelson, M. D.,; C. U. Lowe, M. D. and R. J. Salmon, M. Sc.
Am. J. Dis. Child. 80: 191, 1950

3. Experimental Nutritional Megaloblastic Anemia: Relation of Ascorbic Acid and Pteroylglutamic Acid.
Charles D. May, M. D.; R. D. Sundberg, Ph D.; F. Schaar, M. D.; C. U. Lowe, M. D. and R. J. Salmon, M Sc.
Am. J. Dis. Child. 82: 282-209, 1951.

4. Levine, S. Z., Marples, E. and Gordon, H. H.
Defect in the Metabolism of Aromatic Amino Acids in Premature Infants. Role of Vitamin C
Sci. 90: 620, 1939

5. Levine, S. Z., Marples, E., and Gordon, H. H.
A Defect in the Metabolism of Tyrosine and Phenylalanine in Premature Infants. Identification and Assay of Intermediary Products.
J. Clin. Invest. 20: 199, 1941

6. Levine, S. Z., Gordon, H. H. and Marples, E.
A Defect in Metabolism of Tyrosine and Phenylalanine in Premature Infants. Spontaneous Occurrence and Eradication by Vitamin C.
J. Clin. Invest. 20: 209, 1941

7. Levine, S. Z., Dann, M. and Marples,E.
Demonstration of the Irreversible Conversion of Phenylalanine to Tyrosine in the Human Organism.
J. Clin. Invest. 22: 551, 1943.

8. Levine, S. Z.
Tyrosine and Phenylalanine Metabolism in Infants and the Role of Vitamin C.
Harvey Lect. 42: 303, 1947

TABLE XIV

| Monkey No. | Condition and Therapy | Day[2] of Experiment | Maximum Change[3] in Blood Sugar in First 30 Minutes | Maximum Depression[3] in Blood Sugar Between 30-90 Minutes | Two Hour Blood Sugar / Fasting Blood Sugar |
|---|---|---|---|---|---|
| | INSULIN TOLERANCE TESTS[1] | | | | |
| 33 | Control | | -64% | 66% | 0.53 |
| 52 | Control | | -26% | 32% | 1.15 |
| 118 | Control | | -42% | 43% | 0.68 |
| 134 | "Sick control" | | - 7% | 8% | 1.20 |
| 52 | Adrenalectomized | 25[4] | -78% | 78% | 0.22 |
| 121 | Ascorbic acid deficient | 53 | +11% | 52% | 0.58 |
| 122 | Ascorbic acid deficient | 53 | -64% | 21% | 0.77 |
| 109 | Ascorbic acid deficient | 51 | +56% | 21% | 1.16 |
| 106 | Scorbutic | 58 | +56% | 0% | 1.01 |
| 113 | Scorbutic | 51 | -28% | 48% | 0.65 |
| 113 | Scorbutic and PGA deficient | 60 | +43% | 0% | 1.57 |
| 107 | Scorbutic and PGA deficient | 65 | +47% | 19% | 1.25 |
| 105 | Scorbutic<br>Ascorbic acid, 1 mg, I.M. q.d. | | | | |
| | a. 5 days | 72 | +100% | 8% | 0.96 |
| | b. 25 days | 92 | -25% | 36% | 1.01 |
| 110 | Scorbutic<br>Glutathione, 1 gm, I.M. q.d.<br>3 days | 74 | +57% | 11% | 0.98 |
| 111 | Scorbutic<br>Aminopterin, 0.4 mg )<br>Ascorbic acid, 100 mg) I.M. q.d. 4 days | 74 | -10% | 44% | 0.58 |
| 107 | Scorbutic and PGA deficient<br>Cortisone, 20 mg, I.M. q.d.<br>6 days | 71 | -22% | 48% | 0.53 |
| 113 | Scorbutic and PGA deficient<br>Folinic acid, 2 mg, I.M. q.d.<br>5 days | 72 | +55% | 44% | 0.38 |
| | EPINEPHRINE TOLERANCE TEST | | | | |
| 119 | Ascorbic acid deficient | 45 | +150% | 0% | 1.90 |
| | EPINEPHRINE-INSULIN TOLERANCE TESTS | | | | |
| 125 | Ascorbic acid deficient | 47 | +115% | 0% | 1.02 |
| 52 | Adrenalectomized | 69 | +84% | 0% | 1.30 |

1. For purposes of analysis, the curves obtained in the insulin tolerance tests were divided into three phases: a) a first phase, 0-30 minutes, during which a depression of blood sugar was expected, b) a second phase, 30-90 minutes, at the end of which the action of insulin was assumed to be completed, and c) a third phase, ending at 2 hours, by which time a full recovery of fasting level was expected.
2. The day that ascorbic acid was eliminated from the diet was considered the first day of the experiment.
3. All values listed are expressed as percent change - $\frac{\text{Change}}{\text{Fasting Blood Sugar}} \times 100$
4. Experimental days are numbered from the day of adrenalectomy.

TABLE XV

EOSINOPHILS

| Monkey No. | Condition and Therapy | Fasting Eosinophils Per $mm^3$ | 4 Hour Corticotropin Test: Fasting Eosinophil Count | 4 Hour Corticotropin Test: 4 Hour Eosinophil Count |
|---|---|---|---|---|
| 11 | Control | 319 | 319 | 143 |
| 33 | Control | 407,144,178,255 | 407 | 77 |
| 52 | Control | 180,78,55 | | |
| 116 | Control | 170 | | |
| 117 | Control | 222 | | |
| 123 | Control | 170 | | |
| 125 | Control | 220 | | |
| 126 | Control | 145 | | |
| | Average | 196 | | |
| 11 | Ascorbic acid deficient | 143 | 143 | 77 |
| 24 | Ascorbic acid deficient | 275 | 275 | 55 |
| 105 | Ascorbic acid deficient | 0, 145 | | |
| 107 | Ascorbic acid deficient | 189 | | |
| 110 | Ascorbic acid deficient | 100 | | |
| 127 | Ascorbic acid deficient | 99 | | |
| 128 | Ascorbic acid deficient | 132 | | |
| 129 | Ascorbic acid deficient | 320 | | |
| 130 | Ascorbic acid deficient | 132 | | |
| 131 | Ascorbic acid deficient | 88 | | |
| 132 | Ascorbic acid deficient | 44 | | |
| | Average | 135 | | |
| 11 | Scorbutic | 11 | | |
| 24 | Scorbutic | 99 | 99 | 44 |
| 17 | Scorbutic | 72 | 72 | 22 |
| 105 | Scorbutic | 100 | 100 | 11 |
| 106 | Scorbutic | 22, 44, 55 | 44 | 0 |
| 109 | Scorbutic | 33 | | |
| | Average | 93 | | |
| 17 | Scorbutic and PGA deficient | 0 | | |
| 113 | Scorbutic and PGA deficient | 0 | | |
| | Average | 0 | | |
| 105 | Scorbutic-ascorbic acid 1 mg I.M. daily | | | |
| | a. 14 days | 0 | | |
| | b. 45 days | 165 | | |
| 12 | Scorbutic-ascorbic acid 100 mg I.M. q.d. | | | |
| | a. 0 days | 11 | | |
| | b. 17 days | 242 | | |
| 12 | Scorbutic-folic acid 15 mg I.M. daily | | | |
| | a. 0 days | 11 | | |
| | b. 8 days | 11 | | |
| 24 | Scorbutic-folic acid deficient-folic a acid 15 mg I.M. daily | | | |
| | a. 0 days | 44 | | |
| | b. 14 days | 44 | | |
| 113 | Scorbutic-folic acid deficient-folinic acid 2 mg I.M. daily | | | |
| | a. 0 days | 0 | | |
| | b. 14 days | 0 | | |
| 52 | Adrenalectomized | 11,6,11,11,33,70,66 | | |

9. Govan, C. D. and Gordon, H. H.
The Effect of Pteroylglutamic Acid in the Aromatic Amino Acid Metabolism of Premature Infants
Sci. 109: 333, 1949

10. Sealock, R. R., Ziegler, B. and Driver, R. L.
Relation of Vitamin C to the Metabolism of the Melanin Pigment Precursors: Tyrosine and Dihydroxyphenylalanine
J. Biol. Chem. 128: LXXXIX, 1938

11. Sealock, R. R. and Silberstein, H. E.
Control of Experimental Alcaptonuria by Means of Vitamin C.
Sci. 90: 517, 1939

12. Sealcok, R. R. and Silberstein, H.E.
Excretion of Homogentisic Acid and Other Tyrosine Metabolites by the Vitamin C Deficient Guinea Pig.
J. Biol. Chem 135: 251, 1940

13. Sealock, R. R., Perkinson, J. D. and Basinski, D. H.
Further Analysis of the Role of Ascorbic Acid in Phenylalanine and Tyrosine Metabolism.
J. Biol. Chem. 140: 153, 1941

14. Sealock, R. R.
Effect of Dicarboxylic Acid Administration Upon the Excretion of Tyrosine Metabolites by the Guinea Pig.
J. Biol. Chem. 146: 503, 1942

15. Sealock, R. R. and Ian, T. H.
Dihydroxylphenylalanine Metabolism in the Presence of Kidney and Liver Slices of Normal and Scorbutic Guinea Pigs
J. Biol. Chem. 167: 689, 1947

16. Sealock, R. R. and Goodland, R. L.
Oxidation of l-Tyrosine by Guinea Pig Liver Extracts
J. Biol. Chem. 178: 939, 1949

17. Woodruff, C. W., Cherrington, M. E and Stockell, A. K. and Darby, W. J.
Effect of Pteroylglutamic Acid and Related Compounds Upon Tyrosine Metabolism in the Scorbutic Guinea Pig.
J. Biol. Chem. 178: 861, 1949

18. Painter, H. A. and Zilva, S. S
The Influence of l-Ascorbic Acid on the Rupture of the Benzine Ring of l-Tyrosine Consumed in High Doses by Guinea Pigs.
Biochem. J. 41: 511, 1947

19. Rogers, W. F. and Gardner, F. H.
Tyrosine Metabolism in Human Scurvy
J. Lab. Clin. Med. 34: 1491, 1949

20. Swendseid, M. E., Burton, I. F. and Bethell, F. H.
Excretion of Ketoacids and Hydroxyphenol Compounds in Pernicious Anemia
Proc. Soc. Exp. Biol. Med. 52: 202, 1943

21. Swendseid, M. E., Wandruff, B. and Bethell, F. H.
Urinary Phenols in Pernicious Anemia
J. Lab. Clin. Med. 32: 1242, 1947

22. Dyke, S. C., Della Vida, B. L. and Delikat, E.
Vitamin C Deficiency in "Irresponsive" Pernicious Anemia
Lancet 2: 278, 1942

23. Salmon, R. J. and May, C. D.
Metabolism of Tyrosine in Experimental Megaloblastic Anemia and in Scurvy in the Monkey
J. Lab. Clin. Med. 36: 591, 1950

24. Rodney, G., Swendseid, M. E. and Swanson, A. L.
Tyrosine Oxidation by Livers from Rats with a Sulfasuxidine-induced Pteroylglutamic Acid Deficiency
J. Biol. Chem. 168: 395, 1947

25. Rodney, G., Swendseid, M. E. and Swanson, A. L.
The Role of Pteroylglutamic Acid in Tyrosine Oxidation by Rat Liver Tissue.
J. Biol. Chem. 179: 19, 1949

26. Morris, J. E., Harper, E. R., Goldbloom, A.
The Metabolism of l-Tyrosine in Infantile Scurvy
J. Clin. Invest. 29: 325, 1950

27. Rienits, K. G.
Metabolism of l-Ascorbic Acid and l-Tyrosine in Guinea Pig Liver
J. Biol. Chem. 182: 11, 1950

28. Nichol, C. A. and Welch, A. D.
Synthesis of Citrovorum Factor from Folic Acid by Liver Slices. Augmentation by Ascorbic Acid
Proc. Soc. Exp. Biol. Med. 74: 52, 1950

29. Salmon, R. J. and May, C. D.
The Effect of Folinic Acid (Citrovorum Factor) and of Cortisone on the Metabolism of Tyrosine in the Scorbutic Monkey
Arch. Biochem. Biophysics 32: 221, 1951

30. Ferrero, C.
A Positive Millon Reaction in Suprarenal Insufficiency
Schweiz med. Wchnschr. 80: 492, 1950

31. Levine, S. Z., Barnett, H. L., Bierman, C. W. and McNamara, H.
The Effect of corticotropin and Some Adrenocortical Steroids on the Metabolism of Tyrosine and Phenylalanine in Premature Infants.
Sci. 113: 331, 1951

32. Barron, E. S. G. and Singer, T. P.
Studies in Biological Oxidations - Sulfhydryl Enzymes in Carbohydrate Metabolism
J. Biol. Chem. 157: 221-240, 1945

33. Szent-Gyorgi, A.
Observations on the Function of Peroxidase Systems and the Chemistry of the Adrenal Cortex
Biochemical Journal 22: 1387, 1928.

34. Sayers, M., Sayers, G., White, A. and Long, C. N. H.
The Effect of Pituitary Adrenocorticotrophic Hormone on Cholesterol Content of Rat Adrenal Glands
Proc. Soc. Exp. Biol. & Med. 52: 200, 1943

35. Sayers, G., Sayers, M., Lewis, H. L. and Long, C. N. H.
The Effect of Adrenocorticotrophic Hormone on the Ascorbic Acid and Cholesterol Content of the Rat Adrenal
Proc. Soc. Exp. Biol. & Med. 55: 238, 1944

36. Sayers, G., Sayers, M., Fry, E. G., White, A. and Long, C. N. H.
The Effect of the Adrenotrophic Hormone of the Anterior Pituitary on the Cholesterol Content of the Adrenal Gland
Yale Jour. of Biol. & Med. 16: 361, 1943-44

37. Long, C. N. H. and Fry, E. G.
The Effect of Epinephrine on Adrenal Cholesterol and Ascorbic Acid in Rats
Proc. Soc. Exp. Biol. & Med. 59: 67, 1945

38. Sayers, G., Sayers, M., Tsan-Ying-Liang, and Long, C. N. H.
The Cholesterol and Ascorbic Acid Content of the Adrenal, Liver, Brain and Plasma Following Hemorrhage.
Endocrinology 37: 96, 1945

39. Sayers, G., Sayers, M., Tsan-Ying-Liang, and Long, C. N. H.
The Effect of Pituitary Adrenotrophic Hormone on the Cholesterol and Ascorbic Acid Content of the Adrenal of the Rat and the Guinea Pig
Endocrinology 38: 1, 1946

40. Long, C. N. H.
The Conditions Associated with the Secretion of the Adrenal Cortex.
Federation Proceedings 6: 461, 1947

41. Ludewig, S. and Chanutin, A.
The Adrenal Cholesterol and Ascorbic Acid After Injury.
Endocrinology 41: 135, 1947

42. Jailer, J. W. and Boas, N. F.
The Inability of Epinephrine or corticotropin to Deplete the Ascorbic Acid Content of the Chick Adrenal
Endocrinology 46: 314, 1950

43. Pincus, Gregory
The Hormones
Academic Press, 1948

44. Bloch, K.
The Biological Conversion of Cholesterol to Pregnanediol
J. Biol. Chem. 157: 661, 1945

45. Lowenstein, B. E. and Zwemer, R. L.
The Isolation of a New Active Steroid from the Adrenal Cortex.
Endocrinology 39: 63, 1946

46. Giroud, A. and Santa, N.
Variations Sexuelles Du Cortex et de la Medullo-Surrenale. Variations Ponderales et Taux de L'Acide Ascorbique
Compt. Rend. d. Societe de Biologie 133-134: 420, 1940

47. Giroud, A., Santa, N. and Martinet, Magd.
Variations DeL'Hormone Corticale en Fonction de L'Acide Ascorbique
Compt. Rend. d. Societe de Biologie 134: 23, 1940

48. Giroud, A., Santa, N., Martinet, Magd. and Bellon, M. T.
Dependance de L'Hormone Corticale vis-a-vis de L'Acide Ascorbique
Compt. Rend. d. Societe de Biologie 134: 100, 1940

49. Giroud, A. and Ratsimamanga, A. R.
L'Insuffisance Surrenalienne de L' Avitaminose et de L'Hypovitaminose C
La Presse Medicale 1: 449, 1940

50. Giroud, A.
Les Conditions De La Fonction Cortico-Surrenalienne. Importance De L'Acide Ascorbique
La Presse Medicale 2: 841, 1940

51. Daughaday, W. H., Jaffe, H. and Williams, R. H.
Adrenal Cortical Hormone Excretion in Endocrine and Non-Endocrine Diseases
J. Clin. Endo. 8: 244, 1948

52. Treager, H. S., Gabuzda, G. J., Zamcheck, N. and Davidson, C. S.
Response to corticotropin in Clinical Scurvy
Proc. Soc. 75: 517, 1950

53. Vogt, M.
Ascorbic Acid in Adrenal Blood
J. Physiology 107: 239, 1948

54. Bacchus, H. and Toompas, C. A.
Influence of Vitamin C Pretreatment on the Leucocyte Response of Rats Exposed to Sudden Stress
Science 113: 269, 1951

55. Upton, A. C. and Coon, W. W.
The Effect of Corticotropin and Cortisone on Wound Healing in Normal and Scorbutic Guinea Pigs.
Proc. Soc. 77: 153, 1951

56. Dugal, L. P. and Therein, M.
The Influence of Ascorbic Acid on the Adrenal Weight during Exposure to Cold
Endo. 44: 420, 1949

57. Sayers, G. and Sayers, M.
Regulation of Pituitary Adrenocorticotrophic Activity During the Response of the Rat to Acute Stress
Endo 40: 265, 1947

58. Harkins, H. N. and Long, C. N. H.
Metabolic Changes in Shock After Burns
Am. J. of Physiology 144: 661, 1945

59. Lund, C. C. et. al.
Vitamin Metabolism After Burns
Archives of Surgery 55: 557, 1947

60. Beattie, J.
Metabolic Disturbances After Injury
British Med. Jour. 2: 813, 1947

61. Andrese, W. A., Browne, J. S. L.
Ascorbic Acid Metabolism After Trauma in Man
Can. Med. Assoc. Jour. 55: 425, 1946

62. Quick, A. J.
Hypertrophy of the Adrenal Glands in Scurvy
Proc. Soc. 30: 753, 1933

63. Baldwin, A. R., Longenecker, H. E. and King, C. G.
Tissue Lipids in the Ascorbic Acid Deficient Guinea Pig
Archives of Biochem. 5: 137, 1944

64. Oesterling, M. Jane and Long, C. N. H.
Adrenal Cholesterol in the Scorbutic Guinea Pig
Science 113: 241, 1951

65. Lockwood, J. E. and Hartmann, F. A.
Relationship of the Adrenal Cortex to Vitamins A, B1, and C.
Endo. 17: 501, 1933

66. Schaffenburg, C., Masson, G. M. C. and Corcoran, A. C.
Interrelationships of DCA, Cortisone, and Vitamin C in the Genesis of Mesenchymal Lesions
Proc. Soc. 74: 358, 1950

67. Hyman, G. A., Ragan, C. and Turner, J.C.
The Effect of Cortisone and corticotropin on Experimental Scurvy in the Guinea Pig
Proc. Soc. 75: 470, 1950

68. Nichol, C. A. and Welch, A. D.
Synthesis of Citrovorum Factor From Folic Acid by Liver Slices: Augmentation by Ascorbic Acid
Proc. Soc. 74: 52, 1950

69. Ingbar, S. H., Otto, J. F. and Kass, E.H.
Effect of Corticotropin on Blood Glutathione and Sulfhydryl Content of Liver and Kidney in Rats
Proc. Soc. 77: 20, 1951

70. Barron, E. S. G. and Singer, T. P.
Sulfhydryl Enzymes in Carbohydrate Metabolism
J. of Biol. Chem. 157: 221, 1945

71. Borsook, H., Davenport, H. W., Jeffreys, C. E. P. and Warner, R. C.
The Oxidation of Ascorbic Acid and Its Reduction in Vitro and in Vivo
J. Biol. Chem. 117: 237, 1937

72. Fraser, R. W., Albright, F. and Smith, P. H.
The Value of the Glucose Tolerance Test, the Insulin Tolerance Test, and the Glucose-Insulin Tolerance Test in the Diagnosis of Endocrinologic Disorders of Glucose Metabolism.
J. Clin. Enco. 1: 297, 1941

73. Randolph, T. G.
Differentiation of Leucocytes in the Counting Chamber by Propyleneglycol-aqueous stains
Am. J. Clin. Path., Tech. Section 8: 48, 1944

74. Thorn, G. W.
The Diagnosis and Treatment of Chronic Adrenal Insufficiency
Charles C. Thomas, 1949

75. Influence of Hormones on Enzymes; A Symposium
Science 114: 222, 1951

## II. MEDICAL SCHOOL NEWS

### Coming Events

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| November 1 | The Annual Leo G. Rigler Lecture; "Recent Advances in Equipment for Fluoroscopy," Dr. W. Edward Chamberlain, Professor of Radiology, Temple University Medical School, Philadelphia; Museum of Natural History Auditorium; 8:15 p.m. |
| October 29 - November 3 | Continuation Course in Roentgenology of Chest Diseases for Radiologists |
| November 8 - 10 | Continuation Course in Fractures and Traumatic Surgery for General Physicians |

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### Medical School Faculty Dinner

The Medical School Faculty Dinner, which was held on the evening of Monday, October 8, was attended by more than 400 faculty members and friends of the College of Medical Sciences. Dean Harold S. Diehl in his address reported on the growth of the Medical School and the expansion of its activities in various aspects of education in the medical sciences, medical research, and service. He called attention to the large sums of money granted to the University by private donors and foundations, voluntary societies, and governmental agencies and emphasized that this was an expression of confidence in the ability of our faculty.

The audience was especially happy to learn from Dr. Diehl that work was being resumed on the Mayo Memorial Building and that the revised plan would include a tower of 14 stories. Dr. Diehl also stated that a new unit to be used chiefly for cancer research would also be available and would join the Anatomy Building and Millard Hall. Lantern slides picturing the Mayo Memorial Building as it is now planned and the new cancer research unit proved to be of great interest.

President James L. Morrill spoke for the University, and mentioned the accomplishments of the faculty of the College of Medical Sciences and cited for special praise the distinguished alumni of the College of Medical Sciences who were honored as recipients of the Outstanding Achievement Awards. President Morrill on behalf of the University presented a medal and citation to each of 13 alumni. Recipients of the awards were:

Fred L. Adair, Emeritus Professor of Obstetrics and Gynecology of the University of Chicago
Frank E. Burch, Emeritus Professor of Ophthalmology of the University of Minnesota
Earl R. Carlson, Internationally Known Neurologist, Writer, and Lecturer
Albert J. Chesley, Executive Officer of the Minnesota State Department of Health
Arild E. Hansen, Professor and Chairman of the Department of Pediatrics and Director of the Child Health Program of the University of Texas
Alma C. Haupt, Director of the Nursing Division of the Metropolitan Life Insurance Company
Herman E. Hilleboe, Commissioner of Health, the State of New York
Pearl L. McIver, Chief of the Division of Public Health Nursing of the United States Public Health Service
James E. Perkins, Managing Director of the National Tuberculosis Association
Edith L. Potter, Professor of Pathology of the University of Chicago

MEDICAL SCHOOL NEWS - (Continued)

William P. Shepard, Vice President of the Metropolitan Life Insurance Company and President of the American Public Health Association
Albert M. Snell, Senior Internist, Palo Alto Clinic
Edward L. Tuohy, Chief of Medicine of the Duluth Clinic

The program was closed when Dr. E. T. Bell, Emeritus Professor of Pathology, paid a special tribute to Dean Harold S. Diehl. Dr. Bell presented the University with a portrait of Dean Diehl painted by Mr. Edward Brewer, St. Paul artist. Funds to pay for the portrait were raised by clinical and full time members of the faculty and friends of Dr. Diehl. President Morrill accepted the portrait for the University. Dr. Diehl thanked Dr. Bell and the faculty.

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## Continuation Courses

Dr. Edgar S. Gordon, Associate Professor of Medicine, University of Wisconsin Medical School, delivered the Annual Journal-Lancet Lecture on Wednesday, October 17. His subject was, "Integrated Functions of the Adrenal Cortex." Dr. Gordon also participated in a continuation course on Cortisone and Corticotropin which was presented at the Center for Continuation Study. His subject in the continuation course was, "Corticotropin and Cortisone in Endocrine Disorders." Dr. Edmund B. Flink, Associate Professor, Department of Medicine, and Dr. Randall G. Sprague, Associate Professor, Department of Medicine, Mayo Foundation, Rochester, acted as Chairmen for the course and were joined by other members of the faculty of the University and the Mayo Foundation.

Dr. Morris A. Gordon, Senior Assistant Scientist, Mycology Unit, Communicable Disease Center, Chamblee, Georgia, was the visiting faculty member in a course on Clinical Bacteriology presented for medical technologists at the Center for Continuation Study. Dr. Gordon discussed the subject of "Mycology" and emphasized newer techniques in the recognition of fungi which cause human disease. The course was given with the sponsorship and financial support of the Minnesota Society of Medical Technologists and the American Society of Medical Technologists.

## Faculty News

Dr. Irvine McQuarrie has recently given the Annual Maurice Lamm Blatt Memorial Lecture at Cook County Hospital in Chicago and the Porterfield Lecture presented by the Maryland Academy of General Practice in Baltimore, Maryland, Dr. McQuarrie and Dr. Vernon D. E. Smith, from St. Paul, recently participated as guest speakers at the annual meeting of the Utah State Medical Association.

## New Minnesota Medical Foundation Members

Nathan K. Jensen, M. D., Minneapolis
David Siperstein, M. D., Minneapolis
J. H. Weisberg, M.D., Superior, Wisconsin
Theo. T. Benson, M.D., Grand Forks, N.Dak.
D. C. MacKinnon, M.D., Minneapolis
Bourne Jerome, M.D., Minneapolis
Percy A. Ward, M.D., Minneapolis
John T. Pewters, M.D., Minneapolis
V. C. Kremser, M.D., Amery, Wisconsin
Stella I. Burdett, M.D., Balsam Lake
K. Karl Ford, MD., Amery, Wisconsin
Lewis J. Weller, M.D., Osceola, Wis.
L. O. Simenstad, M.D., Osceola, Wis.
Wm. A. Fischer, M.D., Frederic, Wis.
Walter C. Andrews, M.D., Frederic, Wis.
Theodore M. Berman, M.D., Florida
Richard P. Doe, M.D., California
Carl O. Kohlbry, M.D., Duluth

III. UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
WEEKLY CALENDAR OF EVENTS

Physicians Welcome

October 22 - 27, 1951

## Monday, October 22

### 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; M-109, U. H.

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

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

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

12:30 - Physiology Seminar; The Influence of Salt Mixtures in Mouse Diets; Joseph T. King; 214 Millard Hall.

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

4:00 - Pediatric Seminar; A Scoring System for the Bender-Gestalt Test; Wentworth Quast; Sixth Floor West, U. H.

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

4:30 - Public Health Seminar; 15 Owre (Medical Sciences) Hall.

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

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

### Minneapolis General Hospital

7:30 a.m. Fracture Grand Rounds; Dr. Zierold, Station A.

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

12:30 p.m. Surgery Grand Rounds; Dr. Zierold; Station E.

1:00 - 2:00 X-ray Conference; Classroom, 4th Floor.

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

### Veterans Administration Hospital

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

Monday, October 22 (Cont.)

Veterans Administration Hospital (Cont.)

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

1:00 - Metabolic Disease Rounds; N. E. Jacobson and G. V. Loomis. Bldg. I.

Tuesday, October 23

Medical School and University Hospitals

8:30 - Conference on Diet Endocrines and Cancer; M. B. Visscher; Physiology Library.

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

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

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

12:30 - Selected Topics, Permeability and Metabolism; Nathan Lifson; Physiology Library.

3:15 - 4:20 Gynecology Chart Conference; J. L. McKelvey and Staff; Station 54, U. H.

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

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

5:00 - 6:00 X-ray Conference; Presentation of Cases by General Hospital Staff; Drs. Lipschultz and MacDonald; Eustis Amphitheater.

Ancker Hospital

8:00 - 9:00 Fracture Conference; Auditorium.

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

Minneapolis General Hospital

8:00 - Pediatric Rounds; Dr. Gibbs; 5th Floor Annex.

10:00 - Psychiatric Grand Rounds; J. C. Michael and Staff; 3rd Floor Annex.

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

Veterans Administration Hospital

8:30 - Surgery Staff Seminar; Conference Room, Bldg. I.

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

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

Tuesday, October 23 (Cont.)

Veterans Administration Hospital (Cont.)

1:30 - Liver Rounds; Samuel Nesbitt.

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

3:30 - 4:20 Autopsy Conference; E. T. Bell and Donald Gleason; Conference Room, Bldg. I.

Wednesday, October 24

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; Allen Judd and L. G. Rigler; Todd Amphitheater, U. H.

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

1:30 - Conference on Circulatory and Renal Systems Problems; M. B. Visscher; Physiology Library.

5:00 - 5:50 Urology-Pathological Conference; C. D. Creevy and Staff; Eustis 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; Robert 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

9:30 - Pediatric Rounds; Dr. Platou; 7th Floor Annex.

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

1:30 - Pediatric Rounds; Dr. Huenekens and Dr. Ulstrom; 4th Floor Annex.

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.

Wednesday, October 24 (Cont.)

Veterans Administration Hospital (Cont.)

2:00 - 4:00 Infectious Disease Rounds; Main 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, October 25

Medical School and University Hospitals

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

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

12:30 - Physiological Chemistry Seminar; 214 Millard Hall.

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

3:30 - 4:00 Cardiology X-ray Conference; Heart Hospital Theater.

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

5:00 - 6:00 X-ray Seminar; Subject to be announced; Dr. Erick Poppe, Oslo, Norway; Eustis Amphitheater.

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; Dr. Gibbs; 5th Floor.

8:30 - Neurology Rounds; Dr. Heilig, 4th Floor Annex.

9:00 - Neurology Grand Rounds; J. C. Michael and Staff; Station A.

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

11:30 - Pathology Conference; Main Classroom.

1:00 - 2:00 Fracture - X-ray Conference; Dr. Zierold; Classroom, 4th Floor Annex.

2:00 - Psychiatry Rounds; Dr. Benton; 4th Floor Annex.

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, October 26

### 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.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, 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 Artificial Kidney in the Treatment of Renal Failure; F. John Lewis, Richard Egdahl, Milton P. Reiser, and Frank Raffucci; 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.

4:00 - 5:00 Dermatology Seminar; W-312, U. H.

4:00 - Neurophysiology Seminar; Ernst Gellhorn; 113 Owre Hall, Medical Science Bldg.

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

### Ancker Hospital

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

11:00 - Pediatric-Surgery Conference; Dr. Wyatt, Dr. F. Adams; Classroom, Station I.

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

### Minneapolis General Hospital

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

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

11:00 - Pediatric-Surgery Conference; Drs. Wyatt and F. Adams; Classroom, Sta. I.

12:00 - Surgery-Pathology Conference; Drs. Zierold and Coe; Classroom.

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

Friday, October 26 (Cont.)

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, October 27

Medical School and University Hospitals

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

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

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

9:15 - 10:00 Surgery-Roentgenology Conference; J. Friedman, O. H. Wangensteen and Staff; Todd Amphitheater, U. H.

10:00 - 11:30 Surgery Conference; Anterior Resection for Cancer of the Rectum; Charles Mayo; Todd Amphitheater, U. H.

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

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

11:30 - 12:30 Anatomy Seminar; Studies of Hepatic Ribonucleic Acid in Several Species; W. Lane Williams; 226 Institute of Anatomy.

Minneapolis General Hospital

8:00 - Pediatric Rounds; Dr. Gibbs; 5th Floor.

11:00 - 12:00 Pediatric Clinic; Dr. Thomas and Dr. May; Classroom, 4th Floor Annex.

Veterans Administration Hospital

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

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