The Regents of [illegible]
search Unit, U. S. Naval Hospital, Oakland 14, California.
Research on the Pathological Physiology of the Liver
Laurance W. Kinsell, M.D., Director

9-39-37-2
#3

Quarterly Project Summary, as of 7 March 1949

NAV1.941208.087

Work in Progress

1. S^{35}-labeled-methionine studies: S^{35}-labeled-methionine has been used as a research tool for the evaluation of protein metabolism in general, and for the evaluation of anabolism and catabolism of plasma protein in particular, in various disease states including chronic liver disease, Cushing's syndrome, and idiopathic hypoproteinemia. It is also being utilized to evaluate the effects of certain metabolically active steroid hormones such as testosterone and 11 dehydro 17 hydroxycorticosterone. Data accumulated to date indicate that S^{35}-labeled methionine has great value in human research of this sort and that it may be used in a dose which is well below any possible toxic level. At the present time, doses of 25 or 50 microcuries are being used in tracer fashion. The uptake is studied over many weeks in various individuals on the metabolic ward, under balance study conditions. Findings to date are described in paper #2 (see below).

2. Fat metabolism studies: Evaluation of various aspects of fat metabolism is being pursued as a major part of the program of this laboratory. Work so far performed has shown that certain of the steroid hormonal agents known to be metabolically active have a rather profound effect upon ketone metabolism. Work now under way is designed to show the mechanism of these effects. In connection with this, fundamental research is also being pursued which is designed to provide accurate information as to the rate of renal tubular reabsorption of ketones and of other products of fat catabolism and the rate of ketogenesis from fatty acids under standard conditions (see paper #1).

3. Studies in methionine metabolism, previously reported, are being continued. Present work shows that the administration of 9 gm. of methionine daily to patients with liver damage, results in an elevation of the fasting plasma methionine level, such elevation being proportional to the extent and activity of the liver damage. As a corrolary of these findings, it has also been shown that the administration of

significant doses of methionine to patients with severe liver damage can result in very major toxic manifestation, and that the therapeutic use of this substance must, for the present, be viewed with some concern.

4. Studies concerned with the evaluation of cystine metabolism, under such the same conditions as those already pursued for methionine metabolism, are beginning.

5. Evaluation of the effect of steroid protein anabolic hormones in the therapy of liver disease is being intensively pursued. It has been shown in this laboratory and clinic that when such agents are administered to patients with liver disease in conjunction with a high-protein, very low-sodium intake, striking clinical and chemical benefit is obtained. Part of this work has been pursued on a clinical plane and part has been pursued as an integral portion of over all protein balance studies. An initial report has been published. (see paper #4).

Current Publications and Presentations

Papers 1, 2 & 3 have been submitted for publication; #4 is included as reference.

1. Acceleration of Oxidative Lipolysis in Response to Testosterone: Preliminary Report.
2. Studies in Methionine Metabolism. III. The Fate of Intravenously Administered S35-Labeled-Methionine in a Normal Adult Male, in Patients with Chronic Hepatic Disease, "Idiopathic" Hypoproteinemia, and Cushing's Syndrome.
3. Studies in Methionine Metabolism. II. Fasting Plasma Methionine Levels in Normal and Hepatopathic Individuals in Response to Daily Methionine Ingestion.
4. Factors Affecting Protein Balance in the Presence of Chronic Viral Liver Damage.

OMIT 4

Presentations

1. Current and older experimental data presented to medical and biochemical faculties, Stanford University, University of California and Staff of Veterans Administration Hospital, San Francisco, December, January, and February, 1948-49.
2. Lectures - symposium - Liver Disease - Course under auspices of American College of Physicians, San Francisco, 2/10/49.
3. Lectures - symposium - Endocrinology (calcium, phosphorus, fat, and protein metabolism) - Course under auspices of Association for the Study of Internal Secretions, Oklahoma City, 2/22-26-49. (Some of original data on protein-fat metabolism presented.)
4. Lecture - Calcium-Phosphorus Metabolism - Radiological Society, Los Angeles, 2/27/49.

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Periodic Status Report - 1 October to 31 December 1943

I. Summary of Progress Since Last Report:

A. It has been shown unequivocally that certain metabolically active steroid hormones have a profound effect upon fat catabolism (see MS entitled, "Acceleration of Oxidative Lipolysis in Response to Testosterone: Preliminary Report", forwarded to OMR, Washington, D.C. via OMR, San Francisco Branch under date, we believe, of 12/10/43).
B. Further methionine studies have shown that methionine retention in patients with liver damage, is very marked; that this observation constitutes a sensitive test of liver function; and that, as before noted, such retention produces definite toxic manifestations. These data are contained in a paper which will reach you shortly, and which will be sent to the JCI for publication.
C. Further work with S^{35} labeled methionine has, among other things, shown that a patient with idiopathic hypoproteinemia anabolises at a hyper-normal rate, but subsequently catabolises protein tissue at an even greater rate - with the result of a net protein deficit. Much the same picture has been obtained in a patient with Cushing's syndrome, indicating that the metabolic defect in Cushing's is not anti-anabolism, but excess catabolism.
D. Balance studies with pure pituitary growth hormone (Li) have to date been unsatisfactory because of foreign protein reactions.

Manuscripts relating to the above and to other work are near completion, including data relating to nitrogen-sulfur ratios.

II. Research Completed: As noted in I.

III. Practical Application of Work so far Completed:

The methionine retention procedure appears to be an extremely sensitive test of liver function; perhaps as sensitive, or more so, than the cephalin cholesterol flocculation test and much more dependable.

Further information relating to methionine toxicity is of great practical value.

Acceleration of fat catabolism has vast potential clinical applications.

IV. Plans for Future Work: Further work consists of additional studies in -

A. Fat metabolism - mechanism of acceleration of oxidative lipolysis.
B. Protein metabolism)
C. Methionine metabolism) Intimately interlocked.
D. Studies in growth acceleration and retardation.
E. New studies in cystine metabolism and other factors relative to sulfur metabolism.
F. Application of the preceding to specific metabolic disease, notably liver disease, diabetes, hemochromatosis, and acromegaly.
G. Specific steroid hormone studies.

1/10/44
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