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Notes C-14 studies - normals and patients w/ gout / P. vera / leukemia (labeled uric acid)
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and marked reduction of urinary calcium of from 50–75% or from 129 to 345 mg./day varying with the dose administered, with return to pretreatment levels on cessation of therapy. We observed a concomitant rise of urinary phosphorus, which could be explained in large part by the additional phosphorus ingested with the phytate. No significant changes of either serum calcium, phosphorus or alkaline phosphatase were noted in the direction of osteomalacia, even after one year of treatment. Because of distressing side effects, including nausea, excessive gas and diarrhea, aluminum hydroxide gel was administered concurrently. Careful titration of these two agents made prolonged use feasible in the majority of patients. This combination seems even more rational, since it also tends to reduce the rise of urinary phosphorus observed while on phytate.

A Quantitative Comparison of the Response to Exogenous Thyrotropin in Euthyroid and Thyrotoxic Human Subjects

By *Monte A. Greer and Herbert F. Shull.* Radioisotope Service, V. A. Hospital, Long Beach, and the Department of Medicine, U.C.L.A. School of Medicine and University of Oregon Medical School.

Thyroidal secretion rates were determined in 20 euthyroid and 10 thyrotoxic patients by daily external scintillation counting following administration of 100–300 μC I^{131}. Reaccumulation of I^{131} liberated from the thyroid was blocked by daily administration of 90–180 mg. methimazole. Corollary studies were made of serum PBI^{127} and PBI^{131}. Following baseline studies, gradually increasing doses of intramuscular thyrotropin were given to both groups. The average daily dose at which an increased secretion rate was first seen in the euthyroid patients was 1.75 U.S.P. units, compared to 10 units for the thyrotoxic. In both groups stimulation of thyroidal secretion began well before 24 hours following administration of an effective dose of thyrotropin. A period of inhibition began 24 hours after the last thyrotropin injection. This was transient in 2 of the thyrotoxic patients and one of the euthyroid patients, but persisted for the remainder of the period of study in the other subjects. No qualitative difference in response could be detected between the two groups. The data, while inconclusive in themselves, are believed compatible with the hypothesis that thyrotoxicosis is due to an increased secretion of thyrotropin by the pituitary.

Evaluation of a New Oral Androgen in Neoplastic Diseases

By *John B. Field.* Department of Medicine, School of Medicine, University of Southern California and the Los Angeles County General Hospital.

In the attempt to alter the endocrine environment by administering androgens to female patients with inoperable and advanced tumors, present regimes have limitations. Testosterone must be injected two or three times weekly for long periods of time; the oral methyltestosterone (100–200 mg. daily) is unpredictable in its absorption and is expensive. A new oral agent, 9 α-fluoro-11 β-hydroxy-17αmethyltestosterone, known as fluoxymesterone (Halotestin), has been recently synthesized, and has an apparent oral androgenic activity of about 5–10 times that of methyltestosterone. It has been successfully utilized in male hypogonadism for periods of 4 to 6 months. This compound has now been evaluated in 16 patients with inoperable and, in many cases, advanced neoplastic diseases for periods up to 11 months. The most satisfactory results have been achieved in metastatic carcinoma of the breast. Of 7 such patients, to date 4 have had partial to full remissions from 3 to 11 months, at maintenance doses of from 20 to 30 mg. daily. With doses of from 5 to 15 mg. daily, some early recurrence or exacerbation was seen. A female of 77 years with many pulmonary metastases had slight improvement with testosterone (300 mg./week for 9 weeks), but fluoxymesterone 20 mg. daily induced a considerable subjective and objective remission for more than 5 months. A female of 40 years had complete resolution of numerous skin nodules within 3 weeks of a dose of 30 mg. daily. Two females with widespread advanced metastatic disease did not respond to fluoxymesterone or testosterone and succumbed within 2 to 5 months. One female of 40 years did not respond to oophorectomy or fluoxymesterone but is in a remission with corticosteroids. In three cases of inoperable carcinoma of the ovary with ascites treated with doses of 5 to 30 mg. daily, 2 patients have had partial remissions of 6 months in combination with other therapy; one was a therapeutic failure. Most females given a daily level above 10 or 15 mg. have evidenced signs of androgenicity, although this has been less than in those receiving 300 mg. parenteral testosterone weekly. There have been no other undesirable side effects; as with testosterone, some patients show increased hemoglobin levels.

Uric Acid Metabolism: The Oxidation of Uric Acid in Normal Subjects and Patients with Gout, Polycythemia and Leukemia

By *M. Pollycove, B. M. Tolbert, J. H. Lawrence and D. Harman.* Donner Laboratory and Donner Pavilion, University of California, Berkeley.

Uric acid is regarded as an end product of purine metabolism, requiring excretion for its disposal. Recently, other investigators have demon-

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strated that urinary excretion comprises only about 85% of the daily removal of uric acid. This suggests that some uric acid may be broken down to other compounds or may be further degraded to furnish energy by oxidation. This study was undertaken to determine directly total body uric acid, its daily turnover, and the daily amount of uric acid oxidized to CO_2.

Two normal subjects and four patients with gout and/or polycythemia were studied and patients with leukemia are being studied. They were injected intravenously with 10–30 mg. of uric-2-C^{14} acid, specific activity 1–2.5 μc./mg. The specific activity and total amount of uric acid excreted in the urine, the fecal elimination of C^{14}, and the specific activity and total amount of CO_2 eliminated in the breath were determined following injection. $C^{14}O_2$ measurement was made continuously over representative periods, using an ionization chamber, vibrating reed electrometer, and CO_2 gas analyzer.

Normal subjects had total body pools of 650 and 1100 mg., daily turnover of 510 and 610 mg., urinary excretion of 440 and 510 mg., and oxidation of 55 mg. and 100 mg. uric acid. All the patients with gout and/or polycythemia had increased amounts of uric acid in the body. They also showed greater daily turnover, urinary excretion, and oxidation to CO_2 of uric acid. It was found in all cases that oxidation to CO_2 of the labeled carbon atom requires, on the average, several days.

The results of these measurements of $C^{14}O_2$ show that approximately 10–16% of uric acid formed is oxidized to CO_2, and that uric acid, therefore, is not entirely an end product of purine metabolism. In some patients whose body uric acid is increased, a greater percentage of uric acid is oxidized.

GASTROINTESTINAL SYSTEM

Further Studies on the Effect of Reserpine on Gastric Secretion and Its Possible Site of Action

By *J. Alfred Rider, Joyce Swader, John C. Gibbs, Jere Dersin, Lourdes A. Agcaoili and Hugo C. Moeller.* Gastrointestinal Clinic, Department of Medicine, University of California School of Medicine, San Francisco.

Reserpine has been used clinically with good results to treat a number of diseases or conditions in which anxiety states, tensions and aggressions play a prominent role either in symptomatology or etiology. Our previous studies have shown that a single dose of 0.5 mg. or more of Reserpine will increase volume and free acidity of gastric secretion. This effect increases with dose. A single dose of 0.25 mg. or less has no significant effect. Studies with oral Reserpine gave similar results. Pamine, an effective antisecretory agent, shows little if any blocking effect on the stimulated secretion produced by oral or parenteral Reserpine in amounts greater than 0.5 mg.

A study was made on patients who had no free acid in the basal gastric analysis following a vagotomy or a vagotomy and sympathectomy. As was expected, insulin did not stimulate the production of free HCl. Reserpine in a single parenteral 2.5 mg. dose caused the secretion of free acid; this was less than that obtained with the use of Histalog (analog of histamine).

These studies indicate that Reserpine may have a direct peripheral stimulating effect upon the gastric parietal cells.

Quantitative Analysis of the Radioactive Rose Bengal Test of Liver Function

By *Jerold M. Lowenstein.* Department of Medicine, Stanford University School of Medicine, San Francisco.

A quantitative method has been devised for interpreting the radioactive rose bengal uptake excretion test of liver function. When rose bengal tagged with I^{131} is given intravenously, the rise and fall of radioactivity in the liver can be measured with a gamma-ray detector. The shape of each "uptake excretion curve" is determined by three factors—the uptake and excretion rates (both exponential) and the liver blood pool. These quantities can be found by graphic analysis and are expressed as uptake halftime, excretion halftime and per cent of total blood volume in the liver.

In normal subjects, mean values were, respectively, 9 min., 1.5 hrs., and 18%; in Laennec's cirrhosis, 18 min., 5 hrs., and 32%; in biliary cirrhosis, 28 min., over 24 hrs., and 35%; in obstructive jaundice, 15 min., over 24 hrs., and 23%.

When there is hepatocellular damage, uptake is impaired, and obstruction causes delayed excretion. This analysis quantitates each of these factors and thus enhances the value of the radioactive rose bengal test in differential diagnosis of liver disease.

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