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READ BEFORE THE SCIENTIFIC SESSION

The Relation of Sulfanilamide "Acidosis" to the Specific Inhibition of Carbonic Anhydrase. By W. Barry Wood, Jr. and Cutting B. Favour (introduced by P. H. Long), Baltimore, Md.

The cause of the "acidosis" which accompanies sulfanilamide therapy is not known. Mann and Keilin suggested a possible relationship between the acid-base disturbance and inhibition of carbonic anhydrase. This enzyme, contained in red blood cells, catalyzes the reaction $H_2CO_3 \rightleftarrows CO_2 + H_2O$, and was shown to be specifically inhibited *in vitro* by unsubstituted sulfonamide derivatives ($R\text{-}SO_2NH_2$).

Using the manometric method of Meldrum and Roughton, we have extended the studies of Mann and Keilin and have made the following observations which suggest that sulfanilamide "acidosis" is due to inhibition of carbonic anhydrase:

1. Sulfanilamide added to blood *in vitro* (10 mgm. per cent) reduced the enzymatic activity of the red cells to 1/4 of normal blood diluted 100 times. Sulfapyridine, sulfathiazole, and sulfadiazine did not affect the enzyme.
2. The bloods of all patients receiving sulfanilamide showed low CO_2 combining powers and marked depression of carbonic anhydrase; the bloods of patients taking sulfapyridine, sulfathiazole, and sulfadiazine were normal.
3. By dialysis experiments *in vitro* the reaction between sulfanilamide and carbonic anhydrase was shown to be reversible.
4. When sulfanilamide was injected intravenously into dogs, inhibition of carbonic anhydrase and a marked fall in arterial CO_2 content occurred within two minutes. The lowering of the CO_2 content consistently followed inactivation of the enzyme.

Human Sulfathiazole Sensitivity. Observations upon the Febrile, Leukocytic and Immunologic Response. By Theodore J. Abernethy, Samuel C. Bukantz, and John Minor (introduced by Theodore G. Klumpp), Washington, D. C.

Single doses of sulfonamide drugs were administered to a patient exhibiting fever, rash, and leukocytosis during treatment of lobar pneumonia with sulfathiazole. Two grams of sulfathiazole, on the 6th day of normal temperature following cessation of therapy, induced fever and marked leukocytosis. Appreciable amounts of the drug were detected in the blood 2 hours after its oral administration, but the febrile and leukocytic reactions were delayed for 4 hours. Other blood studies were normal. Similar doses of sulfanilamide and sulfamethylthiazole, although accompanied by identical blood concentration, induced no reaction, while response to sulfapyridine was minimal. That sensitivity had been retained during these negative responses was indicated by the persistence of response to as small a dose of sulfathiazole as 0.5 gram, given subsequently.

Skin tests of the sensitive patient, using saline solutions of the pure drugs, were negative. Attempts have been made to detect antibodies to coupled products of diazotized sulfathiazole and serum albumin, globulin, or resorcinol. Precipitation of these azo-antigens with the sensitized patient's serum, as well as certain unrelated immune sera, has been found to occur. Observations upon the specificity of this reaction and its application to the investigation of toxic manifestations to sulfonamides have been made.

Experimental and Clinical Studies on Gramicidin. By Wallace E. Herrell and Dorothy Heilman (introduced by Dr. B. T. Horton), Rochester, Minn.

A bactericidal substance isolated by Dubos (J. Exper. Med., 1939, 70, 1; Ann. Int. Med., 1940, 13, 2025) from a soil bacillus has a marked bactericidal action against gram-positive bacteria. This substance is toxic for laboratory animals when administered by the intravenous route. We have recently shown that one of the toxic effects of this substance is its hemolytic activity. The crude substance (tyrothricin) consists of two fractions, tyrocidine and gramicidin, as reported by Hotchkiss and Dubos (J. Biol. Chem., 1940, 136, 803). They found gramicidin to be the more active against the gram-positive bacteria.

Further studies in our laboratory have shown that the hemolytic effect of the crude substance is due to the presence of gramicidin. Using the tissue culture technic, we have determined the amounts of tyrocidine and gramicidin necessary to inhibit the growth of a number of strains of common gram-positive pathogenic bacteria. Small amounts of gramicidin (0.0005 to 0.0025 mgm.) inhibit the growth of all strains of pneumococci tested. Slightly larger amounts (0.005 to 0.01 mgm.) are required to inhibit strains of hemolytic streptococci, whereas still larger amounts are necessary to prevent growth of Streptococcus faecalis, Streptococcus viridans, and Staphylococcus. Tyrocidine is much less effective than gramicidin against all of these organisms. These results are drawn from approximately 2000 tissue culture preparations used in this study.

Clinical experiences with the local application of gramicidin in the treatment of infections caused by gram-positive bacteria are reported at this time. Suitable methods of applying this substance locally are also reported.

Observations on the Use of "Gramicidin" (Dubos) in the Treatment of Streptococcal and Staphylococcal Infections. By Charles H. Rammelkamp (by invitation) and Chester S. Keefer, Boston, Mass.

Gramicidin is a bactericidal substance which was extracted from certain soil bacilli by René J. Dubos in 1939.

a matter of considerable importance when diagnosis e obscured by previous administration of iodine. ients with hypermetabolism without hyperthyroid- ound magnesium was uniformly normal. Hyperthy- was excluded in these patients by observations of serum iodine and failure to respond to iodine Except for 5 cases of frank myxedema, in ound magnesium was entirely absent, bound mag- was observed to be below the lowest normal value, cent, in only 4 instances. Collateral clinical and ory evidence is adduced to indicate that these cases ctually represent partial hypothyroidism. relating bound magnesium to iodine in serum sug- ost magnesium may be an integral part of the circu- thyroid hormone, or of the complex in which the functions.

Bound Iodine in Blood Plasma. By WILLIAM T. and (by invitation) A. MERTON BASSETT and H. COONS, Boston, Mass.

ugh hormone in the thyroid gland occurs as thyro- , the protein-bound iodine in the blood plasma of al of the horse was found to reside prominently traditional albumin fraction. The protein-bound is subject to fluctuations, depending upon thyroid . Such fluctuations are due chiefly to the thy- -like moiety thereof. Although the fraction re- g diiodotyrosine may vary proportionately, because small magnitude it contributes very little to the increment. Despite variations in the protein- iodine, the inorganic iodine concentration is rather and approximately constant. These findings suggest the protein-bound moiety of plasma iodine may be as an objective index of circulating thyroid hor- and, indirectly, as a measure of thyroid activity. series of 94 cases was analyzed from this standpoint. two-thirds of them the clinical diagnosis and the metabolic rate were consistent and there was a high lation between the latter and the protein-bound . Of the remaining one-third, the basal metabolic did not clearly reflect the clinical status, whereas the n-bound iodine was more reliable. In hypothyroid- plasma protein-bound iodine was consistently low the thyroxine-like fraction thereof almost nil. Of al interest is the exophthalmic ophthalmoplegia classified as "Graves' disease without hyperthy- m," in which the basal metabolic rate was often normal limits and the plasma protein-bound iodine also normal.

tion of Iodine in the Thyroid as a Differential Criterion in the Diagnosis of Two Types of Graves' Disease. By S. HERTZ and A. ROBERTS (introduced by H. Means), Boston, Mass.

another place a rather extended description of a spe- variety of Graves' disease in which the eye sympto- logy is dissociated from the thyrotoxic element is de- ed by Hertz, Means and Williams. We wish to mit here data bearing on the difference in iodine metabolism in the two types of Graves' disease, as determined by the use of radioactive iodine as a tracer in the study of thyroid physiology. The pattern of collection of the iodine in the thyroid in ordinary Graves' disease follows a definite curve; the collection in the thyroid of the special variety has a differently shaped curve; and both of these are quite separable from the curve for normal patients. In general, the method used was as follows: one milligram of labelled iodine was administered by mouth, and the iodine uptake in the gland was measured at various time intervals by means of a Geiger-Müller counter externally placed over the thyroid.

The Effect of Aluminum Hydroxide Ingestion on the Phosphorus and Calcium Disorders of Hypoparathyroidism. By FULLER ALBRIGHT and (by invitation) CHARLES H. BURNETT, WILLIAM PARSON, and HIRSCH W. SULKOWITCH, Boston, Mass.

Aluminum hydroxide has long been used in the production of experimental rickets in animals. It produces its effect by uniting with phosphates in the gastro-intestinal tract and preventing their absorption. Inasmuch as it has for several years been the opinion of those in this laboratory that the disorder of calcium metabolism in hypoparathyroidism is dependent on a more fundamental disorder in phosphate metabolism, it seemed of interest first to determine whether the administration of aluminum hydroxide would lower the high serum phosphorus level in hypoparathyroidism by preventing phosphate absorption and, secondly, whether it would elevate the low serum calcium value. Such was found to be the case, although the results were not quite those that would have been predicted. The studies include complete metabolic data on one patient.

Replacement of Potassium by Sodium in Muscles of Normal Dogs Receiving Desoxycorticosterone Acetate. By JOSEPH W. FERREBEE, DONALD PARKER, WILLIAM H. CARNES, and MILDRED K. GERITY (by invitation) and DANA W. ATCHLEY and ROBERT F. LOEB, New York, N. Y.

Normal dogs receiving daily subcutaneous injections of 25 milligrams of desoxycorticosterone acetate develop diabetes insipidus and attacks of profound muscular weakness. In experiments on six normal animals it was found that administration of desoxycorticosterone acetate caused an increase in intracellular sodium and a decrease in intracellular potassium of skeletal muscle, but no change in the extracellular water jacket of the muscle, that is, no change in the so-called chloride space. The changes in intracellular sodium and potassium concentrations could be prevented by the administration of potassium chloride which maintained a normal relationship of sodium to potassium in the cell and prevented the occurrence of paralysis. The diabetes insipidus was independent of the muscle electrolyte pattern and developed whether or not the animals were given potassium chloride. The diabetes insipidus could be correlated with the fact that all the animals receiving hormone had an elevation of serum