the inhibiting concentrations were in the same general range (Fig. 6).

The combination of streptomycin and PAS caused no increase in the amount of inhibition on this resistant strain; in fact, there was slightly less inhibition with the combination of 370 μg of streptomycin per cc and 0.3 μg of PAS per cc than with PAS alone (Fig. 7).

Discussion. Relatively low concentrations of para-aminosalicylic acid (PAS) inhibit the growth of virulent human tubercle bacilli *in vitro*. It is worth noting that the concentration of drug necessary to inhibit growth varies considerably with the size of the inoculum. Thus more than 100 $\times$ the amount of drug is necessary to cause inhibition if an inoculum of 1.0 mg of tubercle bacilli per 10 cc of medium is used instead of 0.1 mg. This is not true of streptomycin. In experiments simultaneously carried out with both drugs concentrations of 1.48 μg of streptomycin per cc produced almost complete inhibition of growth using a large inoculum, whereas only slight inhibition was obtained with 100 μg of PAS per cc.

There is no question that the combination of streptomycin and PAS in critical concentrations is more effective than either drug alone if the organism is streptomycin-sensitive. These *in vitro* studies agree with the results of animal experiments, which will be reported elsewhere.

It appears that there is no increase in the inhibitory effect of the combination of streptomycin and PAS on the growth of a streptomycin-resistant strain if the streptomycin alone is ineffective (Fig. 7). If, however, a high concentration of streptomycin causes some inhibition, a combination of this amount of streptomycin with PAS will cause greater inhibition than either drug alone. Thus a streptomycin-resistant strain of virulent human tubercle bacilli, isolated from the lung of a patient on autopsy, was partially inhibited by 370 μg of streptomycin per cc. Using this strain the inhibitory effect of PAS was enhanced by the addition of 370 μg of streptomycin per cc.

Summary. 1. The *in vitro* growth of a virulent strain of human tubercle bacilli, H-37RV, is inhibited by 0.74 μg/cc of streptomycin. 2. The *in vitro* growth of H-37RV is inhibited almost completely by a concentration of 1.2 μg/cc of PAS. 3. A moderately inhibiting concentration of either streptomycin or of PAS when combined with a completely non-inhibiting concentration of the other drug produces a marked enhancement of inhibition of the *in vitro* growth of H-37RV. 4. *In vitro* growth of a resistant strain of human tubercle bacilli, H-37RVNR1 is inhibited by 1.2 μg/cc of PAS. 5. The inhibition of growth of this resistant strain is not enhanced by the addition of streptomycin.

We gratefully acknowledge the generosity of Parke Davis and Company, who supplied the para-aminosalicylic acid.

16447

Vitamin A and Thyroid Iodine after Reticuloendothelial Cell Block.*

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The apparent antagonism between vitamin A and thyroid activity has stimulated investigations designed to clarify further the problem, and to determine the nature of this antagonism. It has been shown[1,2] that excess

* This research was aided by a grant from the Fluid Research Fund of Yale University.

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2 Sadhu, D. P., and Brody, S., *Am. J. Physiol.*, 1947, **149**, 400.

TABLE I.

Series	Body wt (g)	Serum iodine γ/100 ml	Thyroid iodine γ/100 mg	Muscle iodine γ/g	*Vitamin A* Serum I.U.%	*Vitamin A* Liver I.U.%
Control (20 animals)	322	3.21 ± 0.12	90.4 ± 3.3	0.2243 ± 0.0586	85.0	408.0
Experimental (10 animals)	313	2.96 ± 0.48*	107.8 ± 4.8†	0.2485 ± 0.0252	53.2	411.2

* $p < .05$.
† $p < .01$.

vitamin A reduces thyroid size and lowers the hypermetabolism of animals given thyroxine. In studying the mechanism of this action, the authors[3] showed that hypervitaminosis A reduced the protein-bound iodine in the liver and thyroid, and increased the level of protein-bound iodine in the serum of rats. That the low level of hepatic iodine was not due to a general depression of body stores was confirmed by the elevated values obtained in skeletal muscles and in the pituitary gland.

The results described suggest the possibility that the rate of destruction of thyroxine by the liver is reduced, resulting in an increase in circulating thyroxine. It is known that any significant reduction of hepatic tissue, such as in subtotal hepatectomy, increases thyroxine activity[4] possibly by virtue of an elevated value of thyroxine in the blood. Furthermore, because excess vitamin A is stored in the Kupffer cells,[5-8] reducing their absorptive power,[9] it is conceivable that the vitamin impairs hepatic destruction of thyroxine by loading these cells. If this were the case, intraperitoneal injections of India Ink, by a similar mechanism, might furnish results like those obtained in hypervitaminosis A: increased circulating thyroxine and reduced thyroid size, with a decrease in thyroid iodine.

Adult male albino rats, placed on Purina Laboratory chow, were given intraperitoneal injections of 5-8 cc of a 5% suspension of India Ink every other day for 15 days. At the end of this time the livers were deeply stained, enlarged, and exhibited numerous points of adhesion to the peritoneal covering of the stomach and duodenum; microscopically there was widespread loading of the reticuloendothelial cells with the ink. The thyroid was not noticeably enlarged. Vitamin A was determined by the antimony trichloride method, using a Lumetron photoelectric colorimeter and protein-bound iodine was determined by the method of Salter and McKay.‡[10] The results are shown in Table I. The iodine content of the thyroid was significantly increased to 107.8 γ % as contrasted with the control value of 90.4 γ %; it will be noted also that this is not accompanied by any appreciable change in thyroid size. Neither protein-bound serum nor muscle iodine were affected by the experimental conditions.

Serum levels of vitamin A were significantly lower than the normal although the hepatic stores of the vitamin were essentially unchanged. The lack of parallelism between serum and liver values, however, should not be unduly emphasized because low levels in the serum are known to exist in the presence of normal or increased stores of hepatic vita-

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‡ The authors wish to thank Dr. William T. Salter for placing laboratory facilities at their disposal for the iodine determinations.

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min A.[8] The normal level of the latter offers further evidence that the vitamin accumulates appreciably in the reticuloendothelial cells of the liver only when excessive amounts are administered.

The results described above are markedly different from those encountered in hypervitaminosis A. Blockade of the reticuloendothelial cells by India Ink is followed by an increase in protein-bound thyroid iodine, unaccompanied by changes in thyroid weight. It is obvious that if excessive amounts of vitamin A lessen hepatic destruction of thyroxine, this action cannot be due to an accumulation of the vitamin in the reticuloendothelial cells of the liver. That the effects must be explained by a different mechanism is further indicated by the lack of concomitant elevation in circulating thyroxine in the experiments discussed. The dissociation between the latter and protein-bound iodine in the thyroid is of interest because, in normal rats, the level of circulating thyroxine appears to be dependent upon the thyroxine content of the gland and is limited by the capacity of the gland to produce thyroxine.[11]

In view of the normal thyroid weight of our animals, it would seem probable that both production and storage of thyroxine is increased, although it is released in normal amounts into the circulation. Our studies on hypervitaminotic animals suggest that vitamin A may lessen hepatic destruction of thyroxine, with a consequent hyperthyroxinemia and increase in pituitary iodine; the result would be a depression of thyrotropic hormone secretion[12,13] and, eventually, a reduction in thyroid size. No explanations can be advanced as yet for the results described in the present paper. Further studies are necessary to determine the underlying mechanism producing these effects.

Summary. 1. Protein-bound iodine was decreased in the liver and increased in the thyroid after reticuloendothelial cell block; increased production and storage of thyroxine is indicated by the data presented. 2. Hepatic vitamin A was not affected by the experimental conditions, although serum vitamin A was decreased. 3. The bearing of these results on those of hypervitaminosis A is briefly considered.

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16448

Ocular Refractive Changes Accompanying High Blood Sugar in Alloxan-Treated Dogs.

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Disturbances in the vision of diabetic patients are frequently observed which involve no apparent pathological changes in the eye. Since they may be remedied by a suitable correction lens, the phenomenon appears to be one of refractive change. These disturbances may be either in the direction of myopia or hypermetropia. In general, myopic changes are said to occur after the onset of diabetic conditions, but before the start of therapy; hypermetropic changes are said to occur after the start of therapy. Myopia may persist, but hypermetropia is always temporary, the average duration being 2 to 4 weeks.[1-3]

* Aided by a grant from the Research Board of the University of California.

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