0.1 μ g of biotin methyl ester, which shows that the failure to grow in the tubes containing the pimelic acid was because the pimelic acid did not replace biotin, not because the medium was injurious; du Vigneaud and associates obtained maximum growth of the diphtheria bacillus under their experimental conditions with 1.5 μ g of pimelic acid, and a marked effect with 0.05 or 0.1 μ g. Eakin and Eakin, however, used as much as 1 mg of pimelic acid per culture, and report that 20 μ g per 12 ml culture gave maximum results. We obtained no growth from the addition per tube of the basal medium 0.1 mg of pimelic acid and 1 mg of *l*-cystine, or 1 mg of pimelic acid and 1 mg of cystine. Growth was obtained when 0.1 μ g of biotin was added to these media, demonstrating that lack of growth in the media containing pimelic acid was because of insufficient biotin, or physiologically equivalent substances, and not because of too much pimelic acid.

Ashbya (*Nematospora*) *gossypii*, the organism used by Kögl as a means of bioassay in the original isolation of biotin, was also tested.[4] Negative results were obtained when 1 μ g or 100 μ g of pimelic acid were added in place of biotin to 8 ml of a basal medium and when biotin was replaced with 1 μ g or 100 μ g of pimelic acid together with 1 mg of *l*-cystine. The results were negative also when the medium containing pimelic acid or pimelic acid and *l*-cystine was further supplemented with 1.5 mg of casein hydrolysate per tube.

It appears that the thirteen fungi we used are not able to synthesize biotin from pimelic acid, or from pimelic acid and *l*-cystine, under our experimental conditions. This should not be interpreted to mean that other organisms can not construct biotin from pimelic acid and *l*-cystine, nor that pimelic acid is not a precursor of biotin. The relation of microorganisms to thiamine and its thiazole and pyrimidine intermediates have demonstrated that some organisms have no synthetic power for thiamine and require it in molecular form; others have incomplete synthetic power and can construct the vitamin if furnished the proper intermediates, but not otherwise; while still others are able to make thiamine from the minerals and sugar in a basal medium. A somewhat similar situation may exist with regard to biotin. If it does, the fungi we have used appear to require biotin as such.

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[4] *Ashbya* was grown on a modification of the medium used by Kögl and Fries which contains thiamine and *i*-inositol.

THE RH FACTOR AND RACIAL ORIGINS[1]

IN 1940 a new factor (Rh) in human blood was described[2] which is present in the blood cells of about 85 per cent. of white individuals (Rh-positive type). This blood property was found to be inherited as a simple mendelian dominant by a pair of allelic genes, *Rh* and *rh*.[3] Investigations on the distribution of the Rh factor among Negroes in New York City revealed a somewhat lower incidence of the Rh-negative type, while in full-blooded American Indians the Rh-negative type appears to be practically absent.[4] The extension of these studies to other races should yield results of significance from the standpoint of racial origins.

To account for the present distributions of the Rh factor in white individuals and in American Indians, a number of hypotheses could be considered, analogous to those proposed to explain the distribution of the four blood groups. Two main possibilities will be discussed: (1) That man was originally Rh-positive and that the present incidence of the Rh-negative type resulted from mutations from gene *Rh* to gene *rh*. While this might conceivably account for the exceptional occurrence of Rh-negative individuals among American Indians, to explain the higher incidence of the *rh* gene (almost 40 per cent.) in white individuals one would have to postulate an improbably high rate of mutation. (2) Another possibility is that there were originally two or more races, some predominately or exclusively Rh-positive, others Rh-negative, and that by crossing the present distribution of the Rh factor resulted.

Of significance with regard to this problem is the relationship that has been demonstrated by Levine *et al.* between the Rh factor and erythroblastosis foetalis, a disease responsible for a certain number of stillbirths and neonatal deaths.[5, 6, 7, 8, 9] In the typical case, the mother is Rh-negative, the father Rh-positive and the fetus Rh-positive, the latter having inherited the Rh factor from the father. Due presumably to some defect in the placenta, fetal blood es-

[1] From the Serological Laboratory of the Office of the Chief Medical Examiner of New York City. Aided by a grant from the Carnegie Foundation and the Committee on Human Heredity of the National Research Council.

[2] K. Landsteiner and A. S. Wiener, *Proc. Soc. Exp. Biol. and Med.*, 43: 223, 1940.

[3] K. Landsteiner and A. S. Wiener, *Jour. Exp. Med.*, 74: 309, 1941.

[4] K. Landsteiner, A. S. Wiener and G. A. Matson, *Jour. Exp. Med.*, 76: 73, 1942.

[5] P. Levine, E. M. Katzin and L. Burnham, *Jour. Am. Med. Assoc.*, 116: 825, 1941.

[6] P. Levine, P. Vogel, E. M. Katzin and L. Burnham, SCIENCE, 94: 371, 1941.

[7] P. Levine, L. Burnham, E. M. Katzin and P. Vogel, *Am. Jour. Obstet. and Gynec.*, 42: 925, 1941.

[8] L. Burnham, *Am. Jour. Obstet. and Gynec.*, 42: 389, 1941.

[9] A. S. Wiener, *Am. Jour. Clin. Path.*, 12: 302, 1942.

capes into the maternal circulation, and in susceptible individuals the production of anti-Rh isoantibodies results. These antibodies filter through the placenta into the fetus and destroy its blood cells and in that way give rise to the disease.

At first sight, one might conclude that since only Rh-positive babies are affected, this mechanism operates in a selective manner so as to eliminate the Rh-positive type. As a matter of fact, all the affected infants are heterozygous, genotype *Rhrh*, so that equal numbers of *Rh* and *rh* genes are lost every generation. The effect of the loss of these genes over a period of many generations on the distribution of the Rh factor is readily computed as follows:

Let us assume that we are dealing with a population of constant size containing x *Rh* genes and y *rh* genes. The initial distribution of the genes would then be as follows:

$$Rh_0 = \frac{x}{x+y} \qquad rh_0 = \frac{y}{x+y}$$

If the number of fetuses and newborn that die from erythroblastosis during one generation is c, then the distribution of the genes during the second generation would be:

$$Rh_1 = \frac{x-c}{x+y-2c} \qquad rh_1 = \frac{y-c}{x+y-2c}$$

Accordingly, if at the onset the number of *Rh* genes is equal to the number of *rh* genes, this process would have no effect on the relative distributions of the genes. If the incidence of the two genes is unequal, however, the less frequent gene would be affected to a greater extent than the more common gene, so that eventually, other things being equal, over a period of thousands of generations, the incidence of the former would be substantially reduced and it might even be practically eliminated.

These results offer further evidence against the mutation theory as an explanation of the present distribution of the Rh factor in white individuals. Even assuming a rate of mutation from *Rh* to *rh* (or *vice versa*) higher than any so far recorded for *Drosophila* and man, this selective action of isoimmunization against the less frequent gene would effectively prevent a population originally completely Rh-positive from attaining as high an incidence of the Rh-negative type as 15 per cent. On the other hand, if one assumes the existence of populations in the past (and possibly still surviving at the present time) consisting almost exclusively of Rh-negative individuals, then from crosses with other populations consisting largely of Rh-positive persons (like the American Indians) a hybrid population could result with a serological composition resembling that of the white individuals of New York City.

In conclusion, it should be mentioned that, as Haldane[10] and Wyman and Boyd[11] have pointed out, if we go back to Paleolithic times when man was presumably a rare animal, chance probably played a large part in modifying gene frequencies. In large populations, however, chance has only a negligible effect, so that at least during post-glacial times racial mixture must have been the most important factor influencing the frequencies of the genes *Rh* and *rh*.

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[10] J. B. S. Haldane, *Human Biology*, 12: 457, 1940.

[11] L. C. Wyman and W. C. Boyd, *Am. Anthrop.*, 37: 181, 1935.

VITAMIN A AND THE THYROID[1]

THERE is a theory that an antagonism exists between vitamin A and the thyroid. The evidence for this has been collected by Smith and Perman,[2] who have published evidence showing that in short experiments there is some counteraction of thyroxin by carotene. More recently Belasco and Murlin[3] in a somewhat similar experiment showed that vitamin A lowered the metabolic rate of hyperthyroid rats. No very logical reasons have been offered for such antagonism, if it exists, however, and close examination of results so far published reveal many discrepancies. It was felt, therefore, that further study was justified, and the following experiments were performed.

The sleeping metabolic rate was determined for 8 rats, 5 male and 3 female. After the range had been established, each rat was given 200,000 U. S. P. XI units of vitamin A[4] per kilogram daily by stomach tube. The concentrate was in oil solution, and contained negligible amounts of vitamin D. The volume of oil fed was between 0.2 cc and 0.6 cc daily. After 50 days of administration of the vitamin at this level (in one case after 34 days) desiccated thyroid powder, U. S. P. XI, was given in addition to the vitamin. The thyroid was given in amounts ranging from 0.25 to 0.35 gm per kilogram daily as a water suspension by stomach tube. The metabolic rate was determined at weekly intervals throughout. In no case did the vitamin A alone cause any significant alteration in the level of metabolic rate. When thyroid was fed in addition to the vitamin, the mean increase in metabolic rate was 25.5 per cent.

A second group of 4 rats, 3 females and 1 male, was given the same dose of thyroid powder after the range of metabolic rate had been determined. This dose caused a mean elevation of 58 per cent. in the metabolic rate. After this effect had been established, vitamin A was administered in addition to the thyroid,

[1] Part of the expenses of this investigation were borne by a grant from the Nutrition Research Laboratories.

[2] D. C. Smith and J. M. Perman, *Endocrinology*, 27: 110, 1940.

[3] I. J. Belasco and J. R. Murlin, *Jour. Nutr.*, 20: 577, 1940.

[4] Supplied by Atlantic Coast Fisheries.