operations can be resumed. Mr. Ralph Evans, who was formerly operator of some of the telescopes at Oak Ridge, is now involved in other operations; he writes of recent visits to Berlin and other German cities.

The supervision of the observational work at the Oak Ridge station has this year been largely the responsibility of Dr. Bok. The metagalactic surveys with the Metcalf refractor, as well as the systematic patrol of bright stars and bright meteors, and photometric and spectroscopic studies of the Milky Way, have been maintained. The Oak Ridge grounds suffered only slight damage from this year's hurricane. The maintenance of the work at the Climax Station of the Observatory, as at Bloemfontein, has met with personnel difficulties. But both Dr. Paraskevopoulos at the southern station, and Dr. Roberts at the Colorado mountain station, have maintained essentially full operation.

Working with nine photographic telescopes, the Boyden station staff made a new monthly record, 1,218 plates, for July, 1944. Only one night of the month was astronomically useless.

The study of solar phenomenon at Climax continues to yield results of exceptional interest, and we are continually reminded of the advisability of carrying through several developments of equipment and technique in the post-war era, in order that from this nearest of the stars we can enrich our knowledge, both of our own earth and of sunlike stars throughout the Milky Way.

During the past year I have published a revision of the distances of thirty of the globular star clusters and a new estimate of the thickness of the star haze surrounding the galactic system. The Gaposchkins have published, or completed for publication, several papers on interesting variable stars. Each month from the Observatory Dr. Bok issues a mimeographed Astronomical News Letter, which is distributed by the Department of State not only to the embassies and legations abroad for European astronomers, but also to something like a hundred American astronomers who are now away from their observatories and libraries. The material in these Astronomical News Letters comes in part from the astronomical literature of all countries, which we get hold of in one way or another, and in part it is prepared by the astronomers themselves in order to summarize for their colleagues the war-time progress in special astronomical fields. The Harvard Announcement Cards, which carry the "spot news" of astronomy, have been issued in considerable number during the year, notwithstanding the absorption of most American scientists in the war. They have reported Kuiper's discovery of an atmosphere of methane and ammonia on Titan, the large satellite of Saturn; Van Biesbroeck's finding of the star of lowest known candle power; Luyten's finding of a pair of white super-dense dwarf stars; and the discovery of comets by observers in Finland and New Zealand. Harvard's contribution to these discoveries has been only in the providing of some photographic material for others to examine, in the checking of the existence or the motion of some of the comets, and in the routine distribution of the astronomical information.

HARLOW SHAPLEY, *Director*

SPECIAL ARTICLES

THE RHESUS GENE AND THE EFFECT OF CONSANGUINITY

IT is well known that consanguinity increases the proportion of homozygotes. Consequently, individuals homozygous for a recessive gene are found to have a higher proportion of parents who are closely related to each other than the average proportion of close consanguinity for the whole population. Since in general only genes with unfavorable effects stand out sufficiently to become objects of single factor analysis, it has been said, correctly, that marriages between near relatives tend to be unfavorable to the offspring. While such a statement is generally modified by the remark that recessive genes with favorable effects should also be more frequently homozygous in the children from consanguineous unions, no case of such a nature has actually been observed.

There is, however, a human disease of peculiar genetic causation which should be less frequent in offspring from consanguineous marriages. This is caused by the so-called Rh gene. When a mother homozygous for the recessive gene r[1] is pregnant with a child of the heterozygous genotype Rr, it happens in a certain proportion of cases that an antibody originates or already exists in the mother's blood against the R-antigen in the blood of the fetus and that diffusion of the antibody into the circulation of the fetus causes erythroblastosis foetalis, a hemolytic condition often fatal. The genetic prerequisites for the parents of the affected child are that the mother be rr and the father either RR or Rr. Thus, the parents must be of different constitution. Since the

[1] Following R. R. Race, G. L. Taylor, F. W. Ikin and A. M. Prior, *Annals of Eugenics*, 12: 206–215, 1944, the symbols R and r will be used instead of Rh and rh. Furthermore, in the following discussion, all alleles which give a positive reaction with one or more R antisera will be jointly labelled R, in contrast to the allele r which does not cause a positive reaction with any R antiserum.

probability of consanguineous parents being of different constitution is less than that of non-consanguineous parents, marriages between near relatives should result in erythroblastosis less frequently than unselected marriages.

An approximative value of this effect will be calculated for first cousin marriages: Let p be the frequency of the r allele in the population, q that of the R allele ($p+q=1$), and k be a constant denoting the proportion of erythroblastosis actually occurring in cases where the genetic prerequisites regarding the constitution of mother and child are present. The frequency of the disease in the offspring of first cousin marriages can be determined after answering: What is the probability of the cousin of an rr woman being either Rr or RR? If, in Fig. 1, No. 7 is rr, her

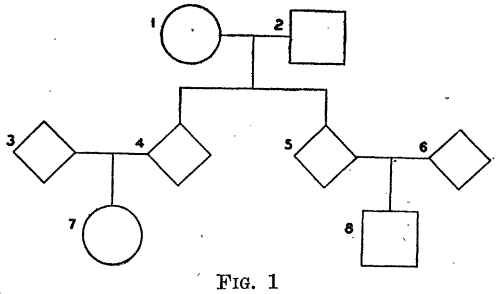

FIG. 1

parent No. 4 must at least have carried one r allele. In this case the two parents of No. 4, namely No. 1 and No. 2, must have carried jointly at least one r allele, while for each of the three other alleles carried by No. 1 and No. 2 the probability of its being r or R is p or q, respectively. Since individual No. 5 obtains a random sample of two of the four parental alleles and transmits only one of these two alleles to No. 8, this latter individual has a chance of one quarter of obtaining any one of the four grandparental alleles. Thus, the total probability of No. 8 inheriting r from No. 1 and No. 2 is one quarter of the certainty, 1, of their possessing one r allele plus three times one quarter of the probability, p, of any of the other three alleles being r:

$$\tfrac{1}{4}+\tfrac{3}{4}p=\tfrac{1}{4}(1+3p)$$

The probability of No. 8 inheriting R from No. 1 and No. 2 is zero for the certain r allele of the grandparents plus three times one quarter of the probability, q, of any of the three other alleles being R:

$$\tfrac{3}{4}q$$

Considering, that the mate No. 6 of No. 5 will transmit R and r to No. 8 in the proportions q and p, the probabilities of the possible genotypes of No. 8 become

$$\text{rr}: \frac{p}{4}(1+3p)$$

$$\text{RR}: \tfrac{3}{4}q^2$$

$$\text{Rr}: \frac{q}{4}(1+3p)+\tfrac{3}{4}pq=\frac{q}{4}(1+6p)$$

The probability of obtaining erythroblastotic children from a mating of No. 8 with the rr cousin, No. 7, is the sum of the probability of No. 8 being RR and one half of that of No. 8 being Rr, times the constant k:

$$k\left[\tfrac{3}{4}q^2+\tfrac{1}{8}q(1+6p)\right]=\tfrac{7}{8}kq$$

Thus, cousin marriages in which the female partner is rr should produce only $\frac{7}{8}$ of the incidence of erythroblastosis as compared with marriages of rr women to non-related men.

If x is the frequency of cousin marriages in the population, the frequency of erythroblastosis in the offspring of cousins is

$$\tfrac{7}{8}k\cdot x\cdot p^2\cdot q \qquad (1)$$

The probability of the disease in non-related marriages is

$$k(1-x)\cdot p^2\cdot q$$

which for small values of x becomes

$$k\cdot p^2\cdot q \qquad (2)$$

The proportion of cousin marriages among the parents of all erythroblastotic children is, using (1) and (2)

$$\frac{\tfrac{7}{8}k\cdot x\cdot p^2\cdot q}{\tfrac{7}{8}k\cdot x\cdot p^2\cdot q+k\cdot p^2\cdot q}$$

which reduces to

$$\frac{x}{x+8/7} \qquad (3)$$

Table 1 gives the values of this expression for various frequencies of cousin marriages. The table shows

TABLE 1

EXPECTED PER CENT. FREQUENCY, e, OF FIRST COUSIN MARRIAGES AMONG THE PARENTS OF ERYTHROBLASTOTIC CHILDREN FOR VARYING VALUES OF PER CENT. FREQUENCY x OF COUSIN MARRIAGES IN THE GENERAL POPULATION

x	.1	.3	.5	.8	1.0
e	.0874	.262	.436	.695	.868

the expected decrease in the number of cousin marriages giving rise to erythroblastosis as compared to the respective assumed value, x, for cousin marriages in the general population. The amount of the difference is not very large, being about 13 per cent. in the whole range of frequencies of cousin marriages as found usually in European and American populations.

A more accurate analysis of the situation would have to take into account, besides other corrections, the fact that among the children of the pairs No. 1 and No. 2, No. 3 and No. 4, and No. 5 and No. 6, fatal cases of erythroblastosis occur. In populations with $q > p$ this further decreases the probability of No. 8 obtaining an R gene from No. 1 or No. 2. Since, however, the incidence of erythroblastosis in its various clinical aspects is only a small fraction of that genetically expected, and since only approximately one half of the affected children die, a factor k^1 for selective mortality introduced into the calculation

would be of the order of .01 and would not appreciably alter the values obtained from the above treatment.

It is doubtful whether differences as small as those calculated in Table 1 could be discovered in the available data of erythroblastosis. Nevertheless, an investigation of the incidence of cousin marriages among the parents of erythroblastotic children and among their maternal grandparents would be of interest, since it is conceivable that it might uncover a higher incidence in either the parents or maternal grandparents or in both than in the general population.[2] If such a higher frequency were found, it would indicate that rare recessive genes on other loci than the R locus share responsibility for the appearance of the disease. If the parents of erythroblastotic children should show an abnormally high incidence of consanguinity, recessive genes concerned with anatomical or physiological properties of the fetus and its membranes would be implied. If the maternal grandparents were consanguineous in an abnormally high frequency, recessive genes concerned with properties of the mother would be suggested.

SUMMARY

It is pointed out that consanguinity among the parents of children affected by erythroblastosis foetalis should be less than in the general population, unless other loci than the R locus are involved in the disease.

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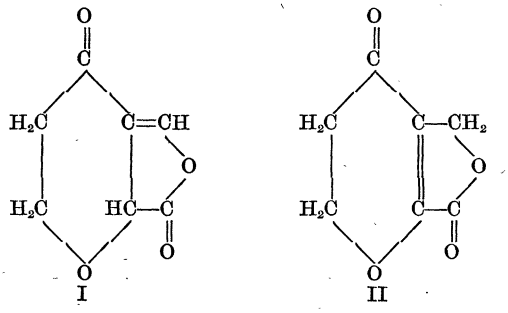
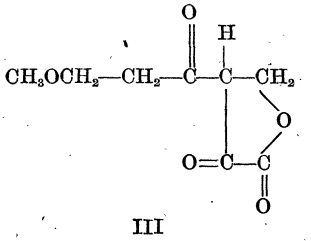
THE SYNTHESIS OF A CLAVACIN ISOMER

A NUMBER of investigators have isolated antibiotic substances from *Aspergillus clavatus*,[1,2] *Penicillium claviforme*,[3] *Penicillium patulum*,[4] *Penicillium expansum*[5] and *Aspergillus giganteus*,[6] which were subsequently found to be identical.[7,8] This mold metabolite has been named clavacin, claviformin, clavatin and patulin. Raistrick[4] *et al.* investigated the chemistry of this product and on the basis of degradation products gave it structure I.



I II

The possibility that tautomerism exists between Formula I and II led us to attempt the synthesis of II. Recently Bergel[9] *et al.* suggested such a tautomerism in order to explain certain of their results on the degradation of clavacin. Prior to the appearance of the publication by Bergel and co-workers we had synthesized compound II in the following manner: ethyl oxalate was condensed with 3-ketobutyl methyl ether in the presence of sodium methoxide to give ethyl-2,4-diketo-6-methoxy caproate, b.p. 124–126° C., 7–8 mm. This product was condensed with aqueous formaldehyde in the presence of an equivalent of alkali to give β-methoxypropionyl-ketoparacone of structure III, m.p. 126° C., C found 51.68, 51.48, calc. 51.61, H found 5.86, 5.50, calc. 5.38.



III

The same product was obtained when methyl vinyl ketone was condensed with ethyl oxalate in the presence of sodium methoxide, followed by the condensation of the resulting sodium salt with formaldehyde.

By treatment of Compound III with 20 per cent. sulfuric acid, methyl alcohol was eliminated to give anhydro-3-hydroxymethyl-5,6-dihydro-γ-pyrone-carboxylic acid-2 (II), m.p. 87° C., C found 54.74, 54.45, calc. 54.55, H found 4.03, 4.01, calc. 3.90.

The ultraviolet absorption spectrum of II has a single maximum at 2,760 Å, the same as clavacin[10] (I), but its intensity ($E^{1\%}_{1\,cm.}$ 613.2) is lower than that of clavacin ($E^{1\%}_{1\,cm.}$ 900–1400[10]).

[2] Data compiled by M. T. Macklin, *Am. Jour. of Diseases of Children*, 53: 1245–1267, 1937, will have to be enlarged before any conclusion can be drawn.
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