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STUDIORUM PROGRESSUS

Concepts of Gene-Structure and Gene-Action Derived from Tetrad Analysis of Saccharomyces[1]

By CARL C. LINDEGREN[2]

Mendelian Procedure. MENDEL conceived of the gene as a stable particle occurring singly in each sex cell and in pairs in the hybrid formed by the fusion of two sex cells. The transmission of genes was analyzed by the distribution of hereditary characters among the progeny of hybrids. The distribution of complementary, mutually exclusive, characters such as brown and blue eyes among the members of a pedigree are the basic data of the geneticist. In higher plants and animals the characteristics can only be diagnosed in organisms carrying two genes–one from each parent. The paired genes are given arbitrary designations (A/a). Since *pairs* of genes are involved, there are three kinds of individuals with regard to a given gene-pair: Aa, AA and aa. The following matings can be made between individuals differing with regard to a single pair: AA × AA, Aa × Aa, aa × aa, AA × aa, AA × Aa, Aa × aa. Predictions concerning the expected frequencies of the different types of offspring are worked out by a "checkerboard" diagram. In the most complex mating (Aa × Aa), each diploid parent can form 2 kinds of sex cells, A and a.

		Sex cells of an Aa male	
		A	a
Sex cells of	A	AA	Aa
an Aa female	a	Aa	aa

The diagram shows that three kinds of offspring are expected in the ratio of 1AA:2Aa:1aa, if each hybrid produced equivalent numbers of A and a gametes. The gene for brown eyes (A) is dominant to the recessive gene for blue eyes (a); both AA and Aa individuals are brown-eyed and indistinguishable. Their genetical constitutions can only be determined by the kinds of offspring which they produce. An Aa × Aa mating will yield some blue-eyed (aa) offspring while an AA × AA (or AA × Aa, or AA × aa) mating yields only brown-eyed offspring. The characteristics of the sex cells were inferred from the kinds of mature plants and animals produced; no direct data on the composition of the sex cells themselves were available. It was concluded that interaction does not occur between the two complementary members of a gene pair (A/a) in the hybrid but that each gene maintains its integrity throughout the life cycle.

"Good" Mendelian Genes. Geneticists frequently speak of genes as if they fall into two natural categories: "good" and "bad". A "good" gene is easy to diagnose (especially in combinations with others), is relatively unaffected by environment, does not diminish vigor to an unusual extent, and usually gives regular ratios. "Bad" genes have one or more of the opposite characteristics. Classical Mendelian genetics is based on the analysis of data involving hybrids carrying "good" genes. Genetical analysis of a species with too many "bad" genes is difficult, if not impossible, along classical lines; geneticists often say that such organisms are "poor" genetical material and therefore cannot be studied properly. Even in the "best" species, characters are found which, although obviously gene-controlled, do not behave regularly. Genes controlling characters of this type were "bred out" of stocks, since they complicate linkage calculations. Pioneer geneticists concentrated on the study of genes which had been selected for regularity of behavior. The preference of the pioneer geneticist for the stable genes is no more reprehensible than the preference of the biochemist for easily crystallizable enzymes. The fact that he dealt almost exclusively with stable characters helps to explain his conviction that interaction between alleles does not occur in a heterozygous hybrid.

Tetrad Analysis. In sexual reproduction the sex cells are formed during the reduction divisions in which a single hybrid cell forms a tetrad of four cells each with a single set of chromosomes. Actually, if the basic assumption of the Mendelian theory is correct, and each tetrad produced by a hybrid male contains 2A and 2a sperm, each tetrad should be represented as AAaa. Since only the mature progeny (AA, Aa or aa) can be characterized, a direct test of this assumption is not possible using maize or *Drosophila.* Let us suppose that, instead of only AAaa tetrads, five different kinds of tetrads were formed by an Aa heterozygote (AAAA, AAAa, AAaa, Aaaa, and aaaa). If the complementary types (AAAA, aaaa, and AAAa, Aaaa) occurred in equal numbers, the sex cells produced by the male would be half A and half a in agreement with the checkerboard diagram.

This hypothetical case reveals that, in the absence of direct tetrad analysis, the conclusion that all tetrads are regularly Mendelian is purely inferential. When an aa individual is mated to an Aa hybrid and the offspring are half of the dominant type (Aa) and half of the recessive type (aa), it can be concluded that half of the sex cells of the hybrid carried the dominant gene (A) and half carried the recessive gene (a). The further inference that each hybrid cell produced an AAaa tetrad is not justified. If five different types of tetrads were produced, a statistical equivalence of A and a sex cells could result. Since the view that genes in a hybrid do not interact is based on this inference, direct tetrad analysis is required to test its validity.

Gene Conversion

A striking advantage of yeasts[1] and other fungi is their adaptability to direct tetrad analysis (Fig. 1). Four spores in a single tetrad contain the four nuclei produced by the reduction divisions of a single nucleus and each gives rise to a culture which can be characterized directly without the interference of dominance or recessiveness. Much of the data obtained from direct tetrad analysis of yeasts and other fungi has been consistent with the Mendelian concept, but many exceptions have occurred which cannot be explained on the conventional Mendelian theory.

The theory of gene conversion was first proposed by WINKLER[2] at a time when tetrad analysis was being

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[2] Biological Research Laboratory, Southern Illinois University, Carbondale, Illinois.

[1] CARL C. LINDEGREN, *The Yeast Cell, Its Genetics and Cytology* (Educational Publishers, Inc., St. Louis, 1949).

[2] H. WINKLER, Biol. Zbl. *52*, 163 (1932).

exploited in Europe by KNIEP, BRUNSWICK, and VON WETTSTEIN. WINKLER saw that MENDEL's predictions concerning the ratios expected following reduction were not realized experimentally in *Hymenomycetes* and *Mosses*. At that time the MORGAN school was successfully exploiting *Drosophila* genetics and had no first hand contact with tetrad analyses. The fact that chromosomes could be mapped accurately on the assumption that they broke and reunited by "crossing-over" had been established beyond any reasonable doubt. In Europe, however, *Drosophila* genetics did not have so many adherents, while significant advances were being made in the tetrad analyses of *Hymenomycetes* and *Mosses*. This difference of emphasis in two great centers of genetical study was intensified by the isolation of Germany during the war and made it possible for WINKLER to accept the irregularities encountered by KNIEP as valid justification for rejecting the crossing-over theory; he chose to explain all recombination as the result of gene conversion and hotly defended his views. In 1932 STERN[1] showed that in a *Drosophila* with a chromosome marked visibly at both ends, genetical recombination coincided with the visible occurrence of transfer of the ends of the chromosomes. Although his data prove that chromosomes break and reunite and thereby effect the recombination of genes, they provide no explanation for irregular tetrad ratios and do not apply to the analysis of the tetrads on which WINKLER had based his theory of gene conversion. STERN showed that WINKLER was wrong in proposing that *all* recombination was the result of gene conversion; he did not prove that gene conversion does not occur.

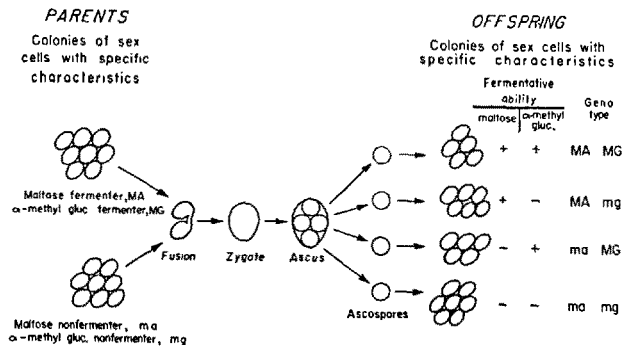

Fig. 1.—Direct tetrad Analysis.

Gene conversion comprises the interaction between alleles (A and a) in a heterozygote (Aa) resulting in either the loss of capacity of a dominant allele (A → a; + → –) or the gain of capacity by a recessive allele (a → A; – → +). The phenomenon of gene conversion in *Saccharomyces* was established by tetrad analysis of yeast hybrids using the gene "markers" controlling ability to ferment maltose and alpha-methyl glucoside. The enzymes involved are highly specific: The gene controlling alpha-methyl glucoside fermentation produces an enzyme which does not act on maltose[2]. The gene controlling maltose fermentation produces an enzyme which does not act on alpha-methyl glucoside. Gene conversion was demonstrable as gain or loss of ability to adapt to and ferment either maltose or alpha-methyl glucoside. For example, hybrid yeasts heterozygous for the ability (and inability) to ferment alpha-methyl glucoside (+/–) often produce tetrads containing one fermenter and three nonfermenters of alpha-methyl glucoside, (+ – – – instead of + + – –) indicating loss at the reduction division by one of the dominant alleles of capacity to ferment alpha-methyl glucoside (+ → –). The reverse (an excess of dominants in a tetrad) occurs less frequently. Conversion has been found in one member of a pair of genes, for example, MG/mg (alpha-methyl glucoside fermentation) without affecting another pair MA/ma (maltose fermentation). Since both of these genes are on the same chromosome, it is concluded that the effect is due to a direct change in the gene itself rather than an anomaly of chromosomal behavior.

MG/mg

MA/ma	++++	+++–	++––	+–––	––––	TOTAL
++++	1 1	2 1	3 2	4 ○	5 ○	4
+++–	6 1	7 1	8 4	9 3	10 ○	9
++––	11 1	12 5	13 171	14 32	15 4	213
+–––	16 ○	17 ○	18 3	19 ○	20 ○	3
––––	21 ○	22 ○	23 ○	24 1	25 ○	1
TOTAL	3	7	180	36	4	230

Fig. 2.—The checkerboard diagram is bounded at the top by the 5 types of asci produced by segregation of MG/mg and bounded on the left by the 5 types of asci produced by the segregation of MA/ma. The squares are numbered from left to right, 1 to 25. The maltese cross formed by the central row and the central column includes the asci in which either MA/ma or MG/mg segregated regularly. The four sets of corner squares cut off by heavy lines contain the tetrads in which irregular segregation of both gene-pairs occurred. The central square (13) contains the tetrads in which both pairs of alleles segregated regularly.

According to Mendelian theory the segregation of a (+/–) heterozygote produces a tetrad with two positive and two negative segregants (+ + – –). All asci heterozygous for MA/ma and MG/mg in which four spores survived and were diagnosed were collected in a single Table and are presented graphically (Fig. 2)[1]. Regular segregations occurred in most asci. Instead of the single type of tetrad expected on Mendelian theory, all five possible types of tetrads (see p. 75) occurred. Since there are five types of tetrads with regard to each pair of characters, 25 different types of tetrads are possible, when both pairs of factors are considered. Each of the different kinds of tetrads is given a specific number (in the upper left hand corner of the squares in Fig. 2). No representatives of some of the combinations appeared. This is indicated by a large zero in the numbered square. Of 230 tetrads 180 segregated regularly (+ + – –) with regard to the ability to ferment alpha-methyl glucoside and 213 segregated regularly (+ + – –) with regard to the ability to ferment maltose. In 171 tetrads both pairs of factors segregated regularly (Fig. 1). Only 4 of the 230

[1] C. STERN, Biol. Zbl. *52*, 67 (1932).

[2] CARL C. LINDEGREN and G. LINDEGREN, Proc. Nat. Acad. Sci. *35*, 23 (1949). – SHLOMO HESTRIN and CARL C. LINDEGREN, Nature *165*, 158 (1950); Arch. Biochem. *29*, 315 (1950); Nature *168*, 913 (1951); Arch. Biochem. Biophys. *38*, 317 (1952).

[1] CARL C. LINDEGREN, J. Genetics (in press).

Genes in Saccharomyces which Control Sugar Fermentation

Sugars	Genes									
Enzyme produced	galacto-kinase	gluco-melibiase	alpha-methyl gluco-sidase	invertase	maltase	alpha-gluco melezitase				
Sugars	GA	ME	MG	SU	MA	MZ	MZ^a	MZ^b	MZ^c	MZ^d
Galactose . . .	+	–	–	–	–	–	–	–	–	–
Sucrose	–	–	–	+	–	+	+	+	+	–
Melibiose . . .	–	+	–	–	–	–	–	–	–	–
Raffinose . . .	–	–	–	+	–	–	–	–	–	–
Alpha-methyl-glucoside . .	–	–	+	–	–	+	–	+	–	–
Maltose	–	–	–	–	+	+	+	+	+	+
Turanose . . .	–	–	–	–	+	+	+	+	+	+
Melezitose . . .	–	–	–	–	–	+	+	–	–	–

tetrads were in the category indicated by the squares 16 to 25, inclusive. These are the asci in which a segregation for maltose follows the pattern + – – – and – – – –. No asci of types 4, 5 and 10 were encountered. These asci are characterized by an excess of maltose-positives and a deficiency of alpha-methyl glucoside-positives. Only 8 of 230 asci were encountered in the four sets of corner squares cut off by the heavy lines, while 222 of the 230 tetrads are confined to the maltese cross formed by the central row and central column. This is the region in which one of the pairs of factors segregates regularly. Irregularities affecting both segregations simultaneously, therefore, are extraordinarily rare. In the segregation of a polyploid, irregularities occur affecting many segregating factors[1]. Since the genes for maltose and alpha-methyl glucoside are on the same chromosome, this type of segregation would also occur in a trisomic. The rarity of simultaneous disturbance of the two different segregations indicates that polyploid and trisomic segregations are either very rare or are absent from this pedigree and do not account for all the non Mendelian behavior.

Inspection of the different families from which these data were obtained showed that they were not homogeneous with regard to the occurrence of irregularities suggesting that the mechanism by which the gene becomes incapable of producing sufficient enzyme to register a positive test is under genetical control. In two of the 25 families only a single type of irregularity was found, namely, that in which a simultaneous excess of dominants of both types occurs in a single ascus. One ascus of type 1 and one of type 2 together with 16 regular asci (type 13), with no other abberations, were found in this group. These two individual tetrads could have arisen from 2 isolated tetraploid zygotes in a family which was otherwise regularly Mendelian.

The high frequency of conversions of MG to mg which is not accompanied by an effect on MA/ma is clear evidence that a non-specific defect in fermentative ability is not involved. The independence of the conversion of MG to mg from effects on MA (on the same chromosome), and the absence of non-specific effects, suggests that conversion is due to an effect directly on the gene.

It was also shown by the study of "late" fermenters that the + and – genes do not differ from each other by a simple qualitative "all or none" difference, but that they differ in a quantitative manner in their potential capacity to mutate. The non fermenter genes which arise by conversion from + to – differ from the more stable – genes in the inbred stock. It was concluded that the "late" cultures are not complete negatives but contain some + substance. "Late" cultures are those which were originally non-fermenters but in which a "spontaneous" vegetative mutation (as contrasted to meiotic conversion) to fermentative ability occurred, and in the presence of the selective medium containing maltose or alpha-methyl glucoside, the mutants increased until they eventually produced a sufficient population to effect delayed but complete fermentation of the substrate. The "late" cultures carry genes which are distinguished by the high frequency with which they achieve the + condition in a medium in which the + gene has a selective advantage. This phenomenon suggests that conversion of + to – frequently involves a partial change which can be reversed.

Gene Conversion in a Multiple Allelic Series

In analyzing the conversion of the maltose and alpha-methyl glucoside genes, a + → – transformation (or the

[1] Carl C. Lindegren and G. Lindegren, J. Gen. Microbiol. *5*, 885 (1951).

Fig. 3.—Comparison of the action of the MZ gene and one of its alleles.

		to produce the enzyme	which acts on
The gene, MZ, is adaptively stimulated by	maltose or turanose or sucrose or alpha-methyl-glucoside or melezitose	alpha-gluco-melezitase	maltose, turanose, sucrose, alpha-methyl glucoside, and melezitose
MZ^d (an allele of MZ) is adaptively stimulated by	either maltose or turanose, *but not by* sucrose or alpha-methyl glucoside or melezitose		

(1) The genes differ only in their ability to respond to the excitation of different sugar molecules. (2) Excitation of the different alleles results in the production of the same enzyme. Therefore, (3) the gene and the enzyme are different and (4) the enzyme is non specifically elicited at some site other than the site of the gene. (5) The union of gene and substrate is the exciting event, the effect of which is transmitted to the site at which enzyme is produced.

reverse) was observed. Much more information can be derived from the analysis of a gene which occurs in a greater variety of states. A series of multiple alleles of the MZ gene exists[1] and the dominant form can be converted into a number of different recessive types.

Familiarity with the different genes controlling sugar fermentation in *Saccharomyces* (Table) was helpful as a background to the genetical analysis of the unusually interesting MZ gene-system. The MZ gene in its fullest potency is capable of responding adaptively to at least 5 different substrates: maltose, turanose, sucrose, melezitose, and alpha-methyl glucoside, but not to raffinose. Exposure to each of these different substrates elicits an adaptive response which results in the production of the same enzyme, alpha-gluco-melezitase, characterized by the ability to attack alpha-glucosides containing a terminal glucose molecule[2]. The multiple alleles of the MZ locus are differentiated by specific losses of fermentative ability. The capacities most easily lost are: (1) ability to ferment the alkyl-alpha-glucoside, alpha-methyl glucoside and (2) ability to ferment the trisaccharide, melezitose. These losses produce cells carrying alleles (1) capable of growing in maltose, turanose, sucrose and melezitose (but not alpha-methyl glucoside) and (2) capable of growing in maltose, turanose, sucrose and alpha-methyl glucoside, but not melezitose. The ability to ferment maltose is rarely lost, and the ability to ferment turanose is usually retained together with the ability to ferment maltose, but turanose is such an expensive sugar that extensive experiments on this point have not been carried out. The ability to ferment sucrose is occasionally lost but is retained more successfully than the ability to ferment either alpha-methyl glucoside or melezitose. A yeast carrying an allele of MZ may be capable of growing in and fermenting maltose but incapable of growing in sucrose, alpha-methyl glucoside or melezitose. After adaptation to maltose, it can ferment sucrose, alpha-methyl glucoside and melezitose. Related experiments have demonstrated that after adaptation to any one of its specific substrates, MZ produces the same enzyme, alpha-gluco-melezitase. The topography of the substrates appears to be involved in the maintenance of fermentative abilities: (1) MZ most frequently loses ability to respond to the two asymmetrical substrates, namely, the alkyl-alpha-glucoside and the trisaccharide, melezitose, but retains its functional activity toward the symmetrical maltose most efficiently. (2) Sucrose inhibits adaptation to maltose by cultures carrying the allele of MZ capable of growing on maltose but incapable of growing on sucrose[2]. (3) Similar inhibitory effects of related compounds occur in the adaptation to maltose and alpha-methyl glucoside[3] of the cultures carrying MA and MG genes. These data suggest that the adaptive reaction of a gene to a substrate corresponds to the capacity of the substrate to fit a topographical surface at the locus of the gene and that this surface may be blocked by substances with related topographies which are incapable of stimulating the production of enzyme.

Enzyme production by MZ is non-specific. This is shown by the fact that a culture capable of adapting to maltose (but incapable of growing on sucrose, alpha-methyl glucoside or melezitose) can produce an enzyme capable of fermenting sucrose, alpha-methyl glucoside and melezitose after adaptation to maltose. This indicates that the gene is not itself the enzyme and that the genes in the allelic series all produce the same enzyme but differ from each other only in their capacity to be excited by different substrates. The enzyme, therefore, is non-specifically elicited, since any one of five different exciters induces the production of the same enzyme.

The production of enzyme by the MZ gene-system is conceived to occur in three steps: (1) The first step, at the site of the gene, involves a reaction between a "receptor" on the gene surface and the adaptive substrate. (2) The final step is the non-specific action of producing enzyme, presumably at a site different from the site of the gene. (3) The reaction between substrate and receptor produces an excitation which initiates enzyme production. Deformation of the gene may render it non-responsive to certain substrates, but does not affect the type of enzyme produced in the final step. Multiple allelism, in this instance, corresponds to a series of specifically different deformations of the receptor of the gene limiting its capacity to respond to the exciting effects of different substrates.

Enzyme Template Genes

The genes controlling sugar fermentation in the Carbondale breeding stock have been specifically selected for the capacity to differentiate "all or none" fermentation. "Non-fermenters" are completely incapable of growing on the substrate or of producing an enzyme capable of acting on the substrate. They may be assumed to differ fundamentally from genes in *Saccharomyces* which are characterized by relatively reduced fermentative activity with regard to carbohydrates. The "all or none" genes have been designated "enzyme-template" genes[1]. An interesting fact in this connection is that mutation from non fermenter to fermenter of galactose occurs only in the presence of galactose; galactose is the mutagen. It is inferred that galactose acts as a specific template for the gene model, and that some non fermenters carry a gene with a deformed template which can be molded into effective shape by contact with galactose. On this view the transferable gene component involved in conversion is a mirror-image[1] of the substrate and the mutagenic action of galactose results from the reshaping of the mirror-image surface of the "receptor" component of the gene by contact with galactose itself.

The Phylogeny of Genes

The genetical analysis of yeasts has also thrown light on the phylogeny of genes since it has been discovered that genes controlling the production of enzymes acting on related substrates are located near each other[2]. The gene MZ is closely linked to the gene MA which controls the ability to ferment maltose. The genes, MA and MG were shown by an experiment involving a cross-over suppressor (presumably an inverted section of a chromosome) to be on the same chromosome, therefore, MA, MZ, and MG are on one chromosome. The gene SU, controlling the fermentation of sucrose and raffinose, is linked to MG in some experiments and is, therefore, also on the MA chromosome. Each of these four genes controls the production of enzymes acting on an alpha glucoside. Each gene produces a different enzyme.

The gene MA controls the fermentation of maltose and turanose by an enzyme which never shows activity toward sucrose, melezitose or alpha-methyl glucoside. It is closely linked to MZ which controls the fermentation

[1] CARL C. LINDEGREN and G. LINDEGREN, Genetics (in press).

[2] N. J. PALLERONI and C. C. LINDEGREN, J. Bact. (in press).

[3] SHLOMO HESTRIN and CARL C. LINDEGREN, Arch. Biochem. *29*, 315 (1950); Arch. Biochem. Biophys. *38*, 317 (1952).

[1] S. EMERSON, Ann. Mo. Bot. Garden *32*, 243 (1945).

[2] CARL C. LINDEGREN and G. LINDEGREN, Nature *170*, 965 (1952).

of maltose, turanose, sucrose, melezitose and alpha-methyl glucoside. This suggests that MZ arose from MA and achieved capacity to ferment sucrose, melezitose and alpha-methyl glucoside, and that the more recently acquired capacities are the more readily lost. The MZ^d allele of MZ resembles MA closely since both confer the ability to adapt to and ferment both maltose and turanose and not sucrose, raffinose, melezitose nor alpha-methyl glucoside. However, cells carrying MZ^d which have been grown on maltose or turanose have the ability to ferment sucrose, melezitose, and alpha-methyl glucoside, while cells carrying MA after growth in maltose or turanose do not acquire significant capacity to ferment sucrose, alpha-methyl glucoside nor melezitose.

KLUYVER[1] pointed out that lactose fermenters are not capable of fermenting maltose and vice versa. The fact that these two characters are mutually exclusive suggests that the gene controlling lactose fermentation is an allele of MA, and that the ability to ferment lactose originated by the transformation of MA into a gene capable of controlling the fermentation of lactose. No breeding experiments have been performed showing that the lactose gene is linked to the others on the maltose chromosome; all attempts to analyze hybrids of lactose and maltose fermenters have been unsuccessful[2].

GA which controls the fermentation of galactose and ME which controls the fermentation of melibiose, a disaccharide containing glucose and galactose, are on the same chromosome. The capacity to ferment galactose is relatively widely distributed among yeast, while the ability to ferment melibiose is relatively rare, and it may be assumed that the original locus was GA. GA and ME are also classified as enzyme-template genes since stocks carrying the recessive allele are completely incapable of utilizing either of these substrates.

Unequal Crossing-Over

The fact that the genes which control the fermentation of closely related sugars are on the same chromosome suggests strongly that they have a common origin. The original gene in the alpha glucoside series may be MA, because the ability to act on maltose is wide-spread throughout the yeasts. Duplicates of the MA locus may have been produced through the mechanism of unequal crossing-over. This phenomenon was originally discovered by STURVEVANT[3]. ALEXANDER and BRIDGES[4] suggested that unequal crossing-over might be important in evolution by making the chromosomes longer through the duplication of small sections. An unequal cross-over near the MA locus would produce one chromosome with two MA genes and one with none. If one "extra" MA locus mutated to a form which conferred the ability to metabolize some other saccharide, the new gene would become a permanent part of the genome. It is assumed that SU, MG and MZ arose from MA in this manner, and that ME may have arisen similarly from GA.

Direct Action of the Gene

It is proposed that the gene exerts its effect by a direct action in the sense that the impingement of an exciter on the surface of the gene results in a single event which stimulates an effector site directly in the production of enzyme. This view differs from the plasmagene theory[1] which considers the possibility that the gene may be stimulated by substrate to cast off a duplicate of itself which acts as the enzyme and multiplies independently of the gene in the presence of substrate. On this theory exposure of the cell to an adaptive substrate would produce a condition resembling the invasion of the cytoplasm by a pathogenic virus.

The plasmagene theory is based on the fact that during adaptation to a specific substrate, the Q_{CO_2} of adapting cells increases in such a manner that the graph of Q_{CO_2} or CO_2 production yields a sigmoid curve. The Q_{CO_2} at a given time was assumed to be a direct measure of the amount of enzyme present, and since the "enzyme" appeared to increase in an autocatalytic manner, it was inferred that the enzyme itself was a self-duplicating particle. It has recently been shown[2] that there is no relation between the shape of the Q_{CO_2} curve and the actual amount of enzyme produced. During early stages of adaptation the adaptive enzyme converts the sugar into stored reserve and considerable amounts of enzyme are present in the cell at a time when little or no CO_2 is being evolved.

The analysis of the MZ gene-system has shown that the gene is not itself the enzyme. This suggests that the gene effects the production of a molecule which confers specificity to the enzyme. The chromosomes lie in the nuclear sap which contains little or no protein and are separated from the cytoplasm by the nuclear membrane which is impermeable to protein. It is proposed that a specificity-conferring molecule produced by gene action diffuses through the nuclear membrane and confers specificity on one of the cytoplasmic proteins. The findings of VON EULER and JANNSON[3] (confirmed by SPIEGELMAN, REINER, and MORGAN[4]) show that galactose adaptation results in the production of an apoenzyme while the coenzyme is present in both unadapted and adapted cells. This makes it seem probable that the specificity-conferring molecule differentiates a cytoplasmic protein and that adaptation is the result of a small change in protein already present rather than the synthesis of new protein.

Gene Reproduction

It may be inferred from the concept of conversion that each locus in a fully potent phenotype carries a large number of transferable gene components distributed in a circlet around the chromosome. Conversion would involve the transfer of these functional components from one locus to another in an unequal manner at the time of reduction. If a relatively large number of the components were required to produce the phenotype, mutation from the non-fermenter to the fermenter could occur, provided an increase in the population of transferable components took place at a more rapid rate than the division of the foundation structure of the chromosome to which they were attached. If each gene is considered as a site to which thousands of functional particles are attached on the outside of an otherwise inert chromosome, the concept of gene reproduction is

[1] A. J. KLUYVER (Thesis, Technische Hogeschoole, Delft, 1914).
[2] CARL C. LINDEGREN, *The Yeast Cell, Its Genetics and Cytology* (Educational Publishers, Inc., St. Louis, *1949*).
[3] A. H. STURTEVANT, Genetics *10*, 117 (1925).
[4] J. ALEXANDER and C. B. BRIDGES in: J. ALEXANDER, *Colloidal Chemistry* (The Chemical Catalog Co., New York, 1928).

[1] S. SPIEGELMAN, Cold Spring Harbor Symp. Quant. Biol. *11*, 256 (1946).
[2] A. L. SHEFFNER, Nature (in press).
[3] H. VON EULER and B. JANNSON, Z. physiol. Chem. *169*, 226 (1927).
[4] S. SPIEGELMAN, JOHN M. REINER, and IDA MORGAN, Arch. Biochem. *13*, 113 (1947).

much simplified. Any longitudinal splitting of the chromosome will partition two qualitatively equivalent parts which may or may not be quantitatively equivalent.

The Autonomy of Cellular Organelles

The capacity of a cell for continuous growth is the result of a specific structural association of the different organelles which make up the cell[1]. Cytological examination of the yeast cell has shown that many of the organelles (the cell wall, the plasma membrane, the mitochondria[2], the nuclear membrane, the centrosome and the centrochromatin) have the same integrity and continuity in time that characterizes the chromosomes; they cannot arise *de novo*. Most of these cellular components divide in a manner which does not provide for precise transmission of specific portions to each daughter cell. The absence of a method for division into two precisely equivalent fractions suggests that they may be relatively homogeneous. There is no reason to assume that one of these cellular components is any more important than any other, or that any one directs the activities of any of the others, except that certain genes are the sole source of their respective enzymes by the enzyme-template mechanism. The cell can function only if all its component parts are present in proper structural correlation and in adequate amounts. There is no reason to assume that any of the components is unique in the manner in which it reproduces itself; the present hypothesis proposes that they all reproduce by the simple accretion of molecules like those which they contain, and it is their association with each other in an adequate milieu which provides the molecules necessary for their increase in size. Control of the growth process could obtain if each of the permanent organelles were rate-limiting; when any one is present in less than the minimal amount, the others cannot obtain the supply of molecules necessary for maintenance and increase until the deficient organelle increases sufficiently to make its required contribution adequate.

The chromosomes differ from the other permanent organelles in their high degree of linear heterogeneity. Mutations usually constitute defects or deletions in the heterogeneous chromosomes. The deficiency in the organism caused by the absence of the contribution ordinarily made by the intact region of the chromosome becomes apparent because the rest of the chromosome produces sufficient material to enable the defective cell to continue to grow, although the result is slightly different from normal. The survival of the defective mutant has led to the view that genes are structures which differ from other cellular components by the specific ability to *reproduce variations of themselves*, but this is fundamentally incorrect. It is correct to say that when a defect occurs in a small segment of a chromosome, the organism can carry on, but in a changed condition, because of the absence of the contribution previously made by that region now called the mutant gene.

Zusammenfassung

Die mit Tetradenanalyse durchgeführten Untersuchungen fordern eine grundsätzliche Modifikation der Mendel-Theorie. Die Experimente führen zur Annahme, dass das Gen eine grosse Zahl übertragbarer Bestandteile trägt, die ringförmig um das Chromosom gelagert sind. Diese Teilchen können bei der Reduktion ungleichmässig auf die Allele verteilt werden. Gewisse Gene werden als «Enzym-Matrizen-Gene» (enzyme-template) bezeichnet, und ihre übertragbaren Bestandteile werden als Spiegelbilder des Substrats aufgefasst. Die Untersuchung einer multiplen Allelserie eines Enzyme-template-Gens ergab, dass das Gen nicht selbst das Enzym darstellt, sondern nur als eine Rezeptorstelle wirkt, die durch die Einwirkung des Substrats angeregt wird. Dies führt zur Bildung des Enzyms.

[1] CARL C. LINDEGREN, Symp. Soc. Exp. Bio. No. 6, 277 (1952).
[2] BALAJI MUNDKUR (in press).

SOCIETATES

I.C.S.U. Abstracting Board

The International Council of Scientific Unions has set up an Abstracting Board (Bureau des Résumés analytiques du C.I.U.S.) with the purpose of facilitating the work of existing well established journals publishing abstracts of original papers in the field of the natural sciences.

In principle, any such journal can seek membership to the Board, which is constituted, under a neutral Chairman, of (a) respresentatives of the interested International Unions, (b) representatives of the Member Journals: together with the Secretary General I.C.S.U. as an *ex officio* member.

A beginning has been made in the field of Physics Abstracting with two Member journals – Physics Abstracts and the Bulletin analytique du C.N.R.S. (France) – represented on the Board of which the present constitution is a follows:

Chairman: Dr. VERNER W. CLAPP, Assistant Librarian, Library of Congress.
Dean ELMER HUTCHISSON, Case Institute of Technology, representing the International Union of Pure and Applied Physics,
Dr. J.H. AWBERY, representing Science Abstracts,
Dr. G. KERSAINT, representing Bulletin analytique du C.N.R.S. (France).
Professor A.V. HILL, Secretary General I.C.S.U.
Secretary: Professor G.A. BOUTRY, Paris.

Dr. L.H. LAMPITT sits as an observer for the International Union of Pure and Applied Chemistry.

The offices of the Secretariat are at the Institut d'Optique, 3, Boulevard Pasteur, Paris XV°, where work has already begun with the aid of a special subvention from UNESCO. The Secretary of the Board will gladly give any information desired about the facilities which can be extended to Member journals.

CONGRESSUS

XIII. Internationaler Kongress der Reinen und Angewandten Chemie in Stockholm

29. Juli bis 4. August 1953

Im Zusammenhang mit diesem Kongress wird ein Symposium der Holzchemie in Stockholm angeordnet, und unmittelbar nach dem Kongress findet ein Symposium der makromolekularen Chemie in Uppsala statt. Die Anmeldungen der Teilnehmer müssen spätestens am 1. März 1953 beim Kongressbüro eingegangen sein. Zirkulare mit dem Kongressprogramm sowie Formulare für die definitive Meldung und sonstige Auskünfte sind vom Generalsekretär erhältlich unter der Adresse: Dr. BENGT SANDBERG, XIII International Congress of Pure and Applied Chemistry, Stockholm 70, Schweden.