The rats on the ordinary bread grew very poorly, gaining on the average only 18 grams in 9 weeks. The rats on extra-yeast bread grew much better, gaining 59 grams on the average in 9 weeks.

The superior nutritive value of the extra-yeast bread was ascribed to its high content of water-soluble B and to the supplemental action of the complete protein of the yeast.

53 (1635)

Evidence for sex-linked lethal factors in man.

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Among the points brought to light during the investigations which followed the rediscovery of Mendel's Law of Heredity were two of especial interest to medical men. These were lethal factors and sex-linked inheritance.

A lethal factor is a Mendelian unit which can be carried by a normal individual as can any recessive, but which when present without its normal allelomorph to balance it, causes the death of the individual possessing it. Among those lethal factors demonstrated for mammals is that for yellow coat color in mice. The color of the wild house mouse is called by geneticists "black agouti." It has as an alternative condition or allelomorph, a type in which almost if not all, black and brown pigment has disappeared from the coat leaving only the yellow pigment unmodified. When black agouti mice are crossed together yellows are never produced. When yellows are crossed together however, yellows and black agoutis are produced in a ratio of 2 to 1. If the yellows had been ordinary mendelian heterozygotes, the ratio should have been 3 to 1, but it is clear that the 2 to 1 ratio is the one involved.

The yellows so produced are never homozygous, as they should be in 33 per cent. of the cases, were unmodified mendelian inheritance involved. The obvious hypothesis is that the homozygous yellow individuals start their development, but perish in early

embryonic stages. This suggestion was therefore made by Castle and Little (1910) and has since been supported by the histological and embryological findings of Kirkham, Ibsen and others.

The case may be diagrammed as follows:

A^y = yellow

A = black agouti.

(Yellow carrying black agouti) × (yellow carrying black agouti)

$A^yA \times A^yA.$

Forms { A^yA^y homozygous yellow dies. / $2A^yA$ yellows carrying black agouti. / AA black agouti.

Sex-linked inheritance is slightly more complicated but has been completely demonstrated. The approximate equality of male and female individuals which characterizes most species of the higher animals, is strongly suggestive of the 1 : 1 mendelian ratio. This ratio is obtained in mendelian inheritance when a DR individual is crossed with either a DD or an RR individual. The condition found in mammals suggests that the female is DD, the male DR in constitution. Evidence for this is derived from the peculiar behavior of certain color characters in inheritance. One of the clearest of these cases is seen in cats. Here black and yellow coat color represent alternative or allelomorphic conditions.

When a black female cat is crossed with a yellow male, two classes of progeny are produced. These are black males and tortoise shell (blotched yellow and black) females. There has been a "criss cross" type of inheritance in which all the sons resemble the mother. This case has been explained on the supposition that there is linkage in inheritance between the factors determining yellow or black coat color and the substances designated X, which are supposed to be intimately connected with the determination of sex.

Thus if B^y = the factor for yellow.

B = the factor for black.

BX BX = black female.

B^yX — = yellow male.

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2 B^yX BX = tortoise-shell females.

2 B^yX — = black males.

Especially interesting are the relations of the colors in the two sexes. It will be noted that in the tortoise-shell females *neither* the yellow factor nor the black factor are completely dominant. They both have a share in the color of the individual and may therefore be considered as balancing each other's activity to some extent. In the male however, the black factor is not balanced by any factor for yellow and thus produces a black coat.

In man it has been shown that several characters, among which are hemophilia and color blindness, depend primarily upon mendelizing units carried in the X or sex chromosome. Their inheritance would, if the hemophilic or color blind condition is recessive, be as follows:

H = normal,
h = hemophilia.

HXHX normal ♀ mated with hX− hemophilic ♂:
Offspring; HXhX− normal female (carrying recessive hmophilia).
HX− normal male.

HXhX heterozygous normal ♀ mated with HX− normal ♂.
HXHX = normal female.
HXhX = normal female (carrying hemophilia).
HX− = normal male.
hX− = hemophilic male.

Lethal factors if sex-linked, follow the same type of inheritance. Thus if L = normal, l = lethal.

LXlX = normal female heterozygous, crossed with LX− normal male.

LXLX = normal female.
LXlX = normal female (heterozygous).
LX− = normal male.
lX− = lethal male (dies).

Since any sex-linked lethal factor in man would, by hypothesis, be borne in the same chromosome as the factor for hemophilia or for color blindness or their normal allelomorphs, it would be linked to them in inheritance. If it were closely linked with the normal allelomorph of hemophilia it would cause the death of the great majority of the normal males which in its absence should occur in equal proportions to hemophilic males. (See diagram above.)

In human families with their relatively small numbers, it would not be at all surprising to find that all the sons in such families would be hemophilic and that by the selective elimination of their normal brothers an excess of hemophilic above the 1 : 1 ratio would be produced. The same would hold true for color blindness.

When a tabulation of the data available in Bulloch and Fildes monograph on hemophilia and at the Eugenics Record Office of the Carnegie Institution of Washington was made such an excess was found to exist even after due allowance is made mathematically for the one hemophilic male occurring in each family. The excess of hemophilics over the expected is so great that the odds are greater than one to a thousand million that it is due solely to chance. The actual numbers are 551 observed to 457 expected. The data available on parallel matings of color blindness are much more meager but offer supporting evidence. The odds are greater than 1 to twenty-six that the result is due solely to chance. The observed number of color blind is 106 and the expected number 90.

In both cases, therefore, in spite of the fact that both hemophilic and color-blind individuals are certainly no better fitted for survival than their normal sibs under equal opportunities, *there is an excess of the abnormal types. This clearly suggests the intervention of a sex-linked lethal factor which eliminates the otherwise "normal" males in certain families and leaves an excess of abnormals.*

Families.	Sex Ratio.		Ratio of Males to 100 Females.	Difference.
	Males.	Females.		
All males hemophilic.....	413	337	122.55 ± 2.73	35.26 ± 3.39
Part males hemophilic.....	1,070	678	157.81 ± 2.02	10.4 × P.E.
All males color blind.....	114	100	114.00 ± 4.4	30.62 ± 6.52
Part males color blind.....	184	119	154.62 ± 4.83	4.6 × P.E.

Another characteristic of sex-linked lethal factors is, that in such forms as man a decreased proportion of female offspring should be produced in the matings in which no such excess of affected males exists. If the families in which *all* males are hemophilic or color blind, are contrasted as regards sex ratio, with those in which *part* of the males are abnormal and part normal a basis for comparison is afforded. Errors of classification, should they occur, should militate *against* finding a significant difference-

and can therefore be disregarded. When such a comparison is made the results are qualitatively similar and give strong support to the evidence already described.

In the cases of hemophilia the odds are enormously against the difference being due solely to chance (one to more than 2,000,000,000) and in the case of color blindness, in spite of the smaller numbers one to more than 500.

Statistical evidence, therefore, strongly indicates the presence of sex-linked lethal factors in man. More complete evidence can be obtained only after an intensive study of several generations of prolific families has been made. The theoretical and practical importance of making such studies is so great that a start on them should be made at the earliest opportunity.

54 (1636)

Acidosis from capillary poisons.

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In a study of pathological conditions of the capillaries, and the effects of these conditions on the body as a whole, we have sought for some agents which produce widespread capillary damage. There is a considerable number of substances classed as capillary poisons. Some of these, for example histamine, produce functional changes, others, such as uranium and diphtheria toxin, produce structural changes. If the change produced results in a damage to the capillary wall, there should be a decrease in its permeability. The tissue cells supplied by the capillary would receive less blood and oxygen, with a resulting abnormal metabolism. It seemed to us that this effect might take the direction of an acidosis. The following figures, obtained from experiments on dogs, the Van Slyke apparatus being used for the alkali reserve determination, bear out this conception.

A study of the table shows that uranium, cantharidin, arsenic, and diphtheria toxin, which cause widespread capillary damage, bring about a definite acidosis. Podophyllotoxin and emetine,