austauschers mit schwefelsauren Gruppen[8] in der H^+-Form jeweils mit einer Lösung geschüttelt, die neben Histamindihydrochlorid auch das Hydrochlorid einer anderen Substanz je in der Valzahl enthielt, die gleich der Kapazität der eingesetzten Menge des Ionenaustauschers war. Nach der Einstellung des Gleichgewichtes wurde durch die Anwendung der mittels potentiometrischer Titration erhaltenen Kurven bestimmt, zu wieviel Prozent die jeweilige Substanz neben Histamin vom Ionenaustauscher aufgenommen worden war[9]. Es wurde so eine durch Prozentwerte charakterisierte Selektivitätsreihe, bezogen auf Histamin als Bezugssubstanz, erhalten, wobei die Zahl also angibt, wieviele von 100 sauren Gruppen des Ionenaustauschers von Gruppen der diesbezüglichen Substanz neben Histamin besetzt worden sind.

Prozentuale Äquivalentverteilung als Mass für die Selektivität gegenüber Histamin am schwefelsauren Dowex-Ionenaustauscher:

(1)	*d*-Glucosamin · HCl	5%
(2)	NH_4Cl	12%
(3)	NaCl	13%
(4)	KCl	15%
(5)	MgCl	17%
(6)	Adenin · 2 HCl	33%
(7)	Adrenalin · HCl	37%
(8)	$CaCl_2$	37%
	Histamin · 2 HCl	50%
(9)	Priscol · HCl	56%
(10)	Mezcalin · HCl	58%
(11)	Tryptamin · HCl	68%
(12)	Pyribenzamin · 2 HCl	76%
(13)	Spermin · 4 HCl	80%
(14)	*n*-Octylamin · HCl	86%
(15)	Privin · HCl	88%
(16)	Antistin · HCl	91%

Alle Substanzen mit Werten oberhalb 50% sind bezüglich unserer Versuchsanordnung als Histaminliberatoren zu bezeichnen. Dieser Befund deckt sich weitgehend mit den im Tierversuch zu beobachtenden Wirkungen, indem unter Vernachlässigung anderer pharmakodynamischer Eigenschaften *in vivo* die gleichen Substanzen als Histaminliberatoren imponieren oder – zumindest an gewissen Rezeptoren – histaminähnlich wirken können. Die unterhalb 50% stehenden Substanzen sind weder im Harzversuch noch allgemein am Tier als typische Histaminliberatoren anzusprechen. Bietet man neben Histamin eine andere Substanz in grossem Überschuss an, so können unter diesen Umständen auch solche Substanzen zu einer Verdrängung von Histamin führen.

Ganz allgemein liefern die bisher vorliegenden Versuchsergebnisse Anhaltspunkte über Austauschvorgänge, wie sie an Depotstrukturen ablaufen dürften: Mit Hilfe einer einfachen Versuchsanordnung lassen sich Verbindungen im Hinblick auf ihr Histaminliberationsvermögen charakterisieren. Ausserdem geben diese Untersuchungen wertvolle Auskünfte über die Resorptionsvorgänge in saurem Milieu gegenüber Ionenaustauschmembranen, wie sie zum Beispiel im Magen anzutreffen sind.

Betrachtet man die angegebene Selektivitätsreihe, so fällt besonders auf, dass die beiden Antihistaminika Antistin und Pyribenzamin als hervorragende Histaminliberatoren erscheinen. Beide Verbindungen vermögen Histamin am schwefelsauren Ionenaustauscherharz zu mehr als 75% einzutauschen. Der Schluss liegt nahe – und er steht nicht im Widerspruch zu *in vivo*-Resultaten –, dass es Verbindungen gibt, die zwar in Depots vorhandenes Histamin freizusetzen, am Erfolgsorgan dagegen die Rezeptorengruppen für den Zugang von Histamin zu sperren vermögen. Dass Antihistaminika Histamin freizusetzen vermögen, wurde übrigens auch von ARUNLAKSHANA[10] in Versuchen an isoliertem Lungengewebe festgestellt, wobei zum Beispiel Benadryl etwa gleich wirksam war wie der bekannte starke Histaminliberator «Compound 48/80». Für eine Testierung von Substanzen im Hinblick auf ihre Fähigkeit, mit biogenen Stoffen (Histamin, Serotonin, Adrenalin, Noradrenalin) in Wechselwirkung zu treten, ist demnach sowohl ein Depotmodell als auch ein Erfolgsmodell notwendig: Austauschversuche an Ionenaustauschsystemen mit Carboxylgruppen (Acrylsäureharze, Speichelmucoproteine, Formylpektine) und mit Ampholytcharakter (Proteine) werden zur Zeit in den Kreis der Untersuchungen einbezogen.

Summary. Mixtures of histamine and other basic substances as hydrochlorides were added in equivalent amounts to an acid ion exchange system containing SO_4-groups in the H^+-form (Dowex 50 W × 2). After completion of the equilibrium, the amounts of both the free histamine and the competing substance were determined by potentiometric titration.

Values are presented for the relative amounts of each substance which are retained by the resin.

The results obtained show that histamine and a given competing substance are selectively distributed on the resin. The method may be useful as a test for the possible histamine-liberating capacity of biologically important substances.

K. KÜTTNER, H. MAJER, G. HUBER und R. JAQUES

Forschungslaboratorium der CIBA Aktiengesellschaft, Pharmazeutische Abteilung, Basel, 21. April 1961.

[8] Dowex 50 W × 2 (200–400 mesh), Kapazität 5 mÄqu./g trockenes Harz.

[9] Weitere methodische Einzelheiten vergleiche K. KÜTTNER, Dissertation Bern (1961).

[10] O. ARUNLAKSHANA, J. Physiol. *119*, 47 P (1953).

STUDIORUM PROGRESSUS

Interaction of *t* Alleles at the *T* Locus in the House Mouse[1,2]

Studies of the complex *T* locus in the 9th chromosome of the house mouse have revealed a series of interesting facts[3]. The interactions of the dominant gene, *T*, with its numerous recessive alleles and of the different recessives with each other are of particular interest. *T* and several of the recessives are lethal when homozygous and the different homozygotes die at different stages in development. *T* in combination with any of these recessive lethal

[1] This work was supported in part by Research Grant B-931 from the National Institutes of Health, U.S. Public Health Service, and in part by a grant-in-aid from the American Cancer Society.

[2] Part of the data reported in this paper were submitted in partial fulfillment of the requirements for the degree of Master of Arts at Bryn Mawr College, Bryn Mawr, Pa., by ANNA C. PAI who would like to express her deepest appreciation to Professor JANE M. OPPENHEIMER for her guidance during the course of the work.

[3] S. GLUECKSOHN-WAELSCH, Cold Spring Harbor Symposia on Quantitative Biology *19*, 41 (1954).

alleles shows complementarity of gene action and heterozygotes are viable and tailless; therefore, matings of tailless animals heterozygous for T and one of these recessive lethal genes represent a balanced lethal system:

	tailless Tt	×	tailless Tt	
TT	Tt		Tt	tt
lethal at 10 days	viable	and	tailless	lethal

Because of this balanced lethal system identification of new t alleles is possible and is based on the fact that different t genes show complementarity of their effects so that compounds of any two different t alleles are viable and normal tailed[4], although males are sterile.

In studies of crosses between the balanced lethal lines A (Tt^0) and 29 (Tt^1), the following results would be expected:

tailless	Tt^0	×	tailless	Tt^1
TT	Tt^0		Tt^1	t^0t^1
lethal	tailless		tailless	normal-tailed viable

Earlier studies[5] have shown that T and t gametes segregate abnormally in the male resulting in an excess of offspring with the recessive t allele. In the present case, such abnormal segregation in the male with an excess of t-gametes should lead in interline crosses to a modification of the expected ratio of 2 tailless: 1 normal-tailed offspring in the direction of 1 tailless: 1 normal-tailed. However, a deficiency rather than an excess of the normal-tailed t^0t^1 compounds was observed by DUNN and GLUECKSOHN-SCHOENHEIMER[6] in studies of crosses between tailless lines A (Tt^0) and 29 (Tt^1), which gave 846 tailless to 359 normal-tailed offspring. They interpreted this small but significant deficiency as being due perhaps to prenatal interaction of t^0 and t^1 resulting in abnormal development and subsequent prenatal death of t^0t^1 embryos, and they offered some preliminary data in support of this hypothesis.

Recently this problem was subjected to further study. Interline matings of animals of several tailless lines, 29, A, 12, 9, 3, gave the results mentioned in Table I.

In these data a deficiency of normal tailed offspring is found in crosses involving tailless lines A, 29, 12, and it is most obvious in the crosses between $Tt^1 \times Tt^0$, in which only 17 of 744 progeny were normal tailed. This deficiency is far in excess of that reported previously and cited above.

Two different tailless lines A (Tt^0) were used in these experiments. Animals of one of these lines (line A1) gave 453 tailless: 1 normal tailed offspring in crosses to animals of tailless line 29. This one normal tailed offspring might well have been the result of a new t mutation the frequency of which DUNN and GLUECKSOHN-WAELSCH[4] calculated to be about one in 500. Mice of the other tailless line A (A2) gave 274 tailless: 16 normal tailed offspring in crosses to tailless line 29. The distribution of the normal tailed offspring among the different litters was as follows: 6 appeared singly, one litter had 5, one litter 3, and another 2 normal tailed viable offspring.

Although we shall not attempt here a further analysis of the difference in frequency of normal tailed offspring in the two different A lines used, one might perhaps speculate that prenatal survival of normal tailed t^0t^1 compounds depends on modifiers which differ in the two A strains. In any case, the frequency of normal tailed compounds in intercrosses of lines A and 29 in the present experiment is considerably lower than that observed in previous interline crosses cited above, and raises the suspicion that the recessive alleles t^0 and t^1 of lines A and 29 no longer show complete complementarity. Consequently, a balanced lethal system seems to exist in crosses between tailless line 29 and tailless line A1, whereas line A2 permits a certain proportion of 'escapers' (HADORN) to survive to term.

Although the greatest deficiency of normal tailed offspring appears in intercrosses of lines 29 and A, crosses of both of these lines to tailless line 12 also resulted in a deficiency, though less pronounced, of normal tailed progeny. In crosses of lines A and 29 to tailless lines 9 and 3, however, no such deficiencies were observed. This indicates that the deficiency of t^0t^1 normal tailed offspring is probably not due to abnormal gametic segregation in the parents, but to interaction of t^0 and t^1 alleles during development. Therefore, the possible embryonic interaction of t^0 and t^1 was subjected to further study.

For this purpose females and males of lines A and 29 were mated with each other. Twenty-seven litters timed by the vaginal plug method were dissected between the 9th and 14th days of gestation. The results are shown in Table II.

Of the 215 embryos studied, 59 were resorbed; 29 did not fall into the easily distinguishable classes of TT (lethal)[7], Tt (tailless)) or normal tailed embryos. These 29 embryos were smaller and less developed than their littermates. Some of them were retarded by approximately 24–48 h in comparison with their normal littermates, but manifested no specific abnormalities and were classified as

Tab. I. Results of interline crosses between tailless lines 29, A, 12, 9, 3

	Tt^1		Tt^0		Tt^{12}		Tt^9		Tt^3	
	o^t	n^t	o^t	n^t	o^t	n^t	o^t	n^t	o^t	n^t
Tt^1			383	13	39	4	113	85	69	93
Tt^0	344	4			29	7	20	7	6	7

Tab. II. Results of dissections of embryos from interline matings of mice of tailless lines A(Tt^0) and 29(Tt^1)

No. of litters	age (days)	T/T	Embryos normal		ab-normal	small	re-sorbed	Total
♀ Tt^1 × ♂ Tt^0								
3	9– 9½	5(4?)	7		2	4	7	25
8	10–10½	9	23		6	4	15	57
			o^t	n^t				
4	11–11½	7	12	3	5	1	6	34
2	12–12½	2	4	—	1	—	4	11
1	13–13½	—	6	—	—	—	2	8
1	14–14½	—	4	—	—	—	7	11
Total 19			26	30 3	14	9	41	146
♀ Tt^0 × ♂ Tt^1								
3	10–10½	4	14		1	3	5	27
			o^t	n^t				
3	11–11½	3	9	6	2	—	3	23
2	13–13½	1	8	—	—	—	10	19
Total 8		8	17	14 6	3	3	18	69

[4] L. C. DUNN and S. GLUECKSOHN-WAELSCH, Genetics *38*, 261 (1953).
[5] L. C. DUNN and S. GLUECKSOHN-SCHOENHEIMER, Genetics *24*, 587 (1939).
[6] L. C. DUNN and S. GLUECKSOHN-SCHOENHEIMER, Genetics *28*, 29 (1943).
[7] P. CHESLEY, J. exp. Zool. *70*, 429 (1935).

'small'; others showed atypical development of the head and neural structures and were classified as 'abnormal'. In view of a certain amount of variation in developmental stages and in size between littermates occurring normally, it is not possible to assign a particular genotype to the 'small' embryos.

DUNN and GLUECKSOHN-SCHOENHEIMER[6] reported that 'abnormal' embryos from crosses of lines A by 29 were smaller and less developed than their tailless littermates and that they had abnormalities involving anterior structures, e.g., microcephaly, microphthalmia, and anencephaly. In the present study of embryos between the ages of 9 and $12^1/_2$ days, 11 were found with head abnormalities, 17 with abnormal neural structures, and 5 with herniated hearts, some of the embryos possessing more than one atypical structure.

Most of the animals with abnormal head structures appeared to be microcephalic and two possessed abnormal mandibular arches. Abnormal neural structures included asymmetrical neural folds in embryos that had not developed beyond the neural fold stage. Two additional embryos had allantois which had apparently failed to join the chorion at earlier stages.

The results of this study as well as of the previous one[6] seem to indicate that interaction of t^0 and t^1 during embryogeny varies in severity. At one extreme, death of t^0t^1 compounds may occur at very early stages, as evidenced by the large number of sites of resorption found in litters of interline crosses on the 9th day of gestation. At the other extreme, some t^0t^1 compounds are viable and normal tailed at term. Between these two extremes spreads the 'abnormal' group with a wide range of abnormalities leading to death of embryos at different stages. This is in distinct contrast to the sharp phase specificity shown by embryos homozygous for either recessive allele which die at definite stages of development[3].

The same lack of sharp phase specificity of effect was reported in an investigation of a group of genetically similar lethal t alleles extracted from different populations of wild house mice, where the homozygous recessive condition of each allele led to a lethal period extending between 8–10 days[8]. Abnormal embryos showed a wide range in degree of differentiation, some developing no farther than the egg cylinder stage, while others formed extraembryonic membranes.

In our present study control embryos for comparison with those dissected from interline crosses were obtained from matings within line 29. Previous investigations had shown the t^1 allele to be a preimplantation lethal[9], but in the present study resorption sites were found for 33 of a total of 85 embryos between $8–12^1/_2$ days, indicating death of such embryos after implantation. Numerically, the proportion of resorbed embryos may well account for the t^1 homozygous class. In addition, the average number of embryonic sites of 9.4 at time of dissection appears rather high for a preimplantation lethal.

These results open the possibility that our tailless line 29 carries a new t allele (t^x) which acts as an early postimplantation lethal and which arose sometime in the past history of our Tt^1 line. Since t^x would be indistinguishable from t^1 in its interaction with T in producing taillessness, it could have been carried through one of the narrow bottlenecks that frequently develop in the course of breeding as difficult a strain as this tailless one with two lethal genes.

If the indications of the presence of a new mutation in line 29 can be confirmed, it would explain some of the differences between earlier studies by DUNN and GLUECKSOHN-SCHOENHEIMER[6], and the present investigation. Therefore, the identification of the recessive alleles involved in the crosses reported here will be the subject of an extensive developmental study.

Zusammenfassung. Mehrfach wurde gezeigt, dass zwei rezessive letale Allele in der Hausmaus (t^0 und t^1) lebensfähige normale Tiere in heterozygoter Kombination t^0/t^1 produzieren. Neuere Daten machen wahrscheinlich, dass das t^1-Allel mutativ abänderte, so dass sowohl seine homozygote Wirkung als auch die Zusammenwirkung mit t^0 beeinflusst worden ist. Hingegen sind Kombinationen von t^0 und dem neuen Allel nicht mehr lebensfähig, und Homozygote sterben erst nach der Implantation.

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Department of Anatomy, Albert Einstein College of Medicine, New York (U.S.A.), March 16, 1961.

[8] D. BENNETT and L. C. DUNN, J. Morph. *103*, 135 (1958).
[9] S. GLUECKSOHN-SCHOENHEIMER, Proc. Soc. exp. Biol. Med. *39*, 267 (1938).

STUDIORUM PROGRESSUS

The Discrimination of Various Cystine Sulfoxides

A controversy exists concerning the constitution of cystine disulfoxide. Based on infrared spectral interpretation, SWEETMAN[1] deemed it to be cysteine thiolsulfonate (I). The isomeric symmetrical disulfoxide structure (II) was advanced by LAVINE and TOENNIES[2] on the basis of its facile reduction to cystine.

LAVINE and TOENNIES[2] have reported the synthesis of cystine disulfoxide by the oxidation of cystine perchlorate with perbenzoic acid in anhydrous acetonitrile. EMILIOZZI and PICHAT[3] have used performic acid in formic acid as the oxidant. It has now been found that both procedures produce both possible isomers. The method of LAVINE and TOENNIES yields mainly the symmetrical disulfoxide, while that of EMILIOZZI and PICHAT affords as main product the thiolsulfonate. The two isomers can be distinguished by their decomposition points, the thiolsulfonate becoming partly viscous above 205°, whereas the symmetrical disulfoxide remains dry and darkens slowly up to 240°.

Both compounds possess a strong peak in the infrared at 8.93 μ. This is the same peak shown by cystine monosulfoxide (Cys(S→O)-S-Cys) (III)[4] and is responsible for the controversial structure assignments. The remaining parts of the spectra are distinctly different (Figure 2).

BREDERECK, WAGNER, BECK, and KLEIN[5] showed recently, with several aromatic sulfoxides, that the band at 1050 cm^{-1} (9.54 μ), which was assigned by SWEETMAN to the sulfoxide group, varies from 1040 cm^{-1} to 1130 cm^{-1} and that various sulfones, disulfones and disulfides exhibit

[1] B. J. SWEETMAN, Nature *183*, 744 (1959).
[2] T. F. LAVINE and G. TOENNIES, J. biol. Chem. *113*, 576 (1936).
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