ERIC F. WIESCHAUS
DOCTOR HONORIS CAUSA



Laudatio Dominae | **Eric F. Wieschaus**

LAUDATIO

PROFESOR ERIC F. WIESCHAUS

Squibb Professor in Molecular Biology, Emeritus,
Professor of Molecular Biology, Emeritus, Lewis-Sigler Institute
for Integrative Genomics, Princeton University,
Laureat al Premiului Nobel pentru Fiziologie sau Medicină, 1995

cu prilejul acordării titlului de
Doctor Honoris Causa al Universității din București

Stimate Domnule Rector,
Stimate Domnule Președinte al Senatului Universității din București,
Stimați colegi, distinși invitați, dragi studenți,

Există momente în viața unei universități în care actul academic depășește rutina și devine un gest de memorie și de recunoaștere. Conferirea titlului de *Doctor Honoris Causa* al Universității din București domnului profesor **Eric F. Wieschaus**, laureat al Premiului Nobel pentru Fiziologie sau Medicină în anul 1995, este unul dintre aceste momente. Este momentul în care comunitatea noastră academică așază alături de tradiția sa de aproape două secole numele unuia dintre cei care, în secolul al XX-lea, au schimbat felul în care înțelegem viața însăși.

I. REPERE BIOGRAFICE ȘI FORMARE ACADEMICĂ

Eric Francis Wieschaus s-a născut la 8 iunie 1947, la South Bend, Indiana, în Statele Unite ale Americii. A urmat studiile de licență în biologie la **University of Notre Dame**, absolvite în anul 1969 cu distincția *magna cum laude*. Și-a continuat formarea științifică la **Yale University**, unde a obținut, în anul 1974, titlul de doctor în biologie, teza sa fiind distinsă cu Premiul John Spangler Nicholas pentru cea mai bună disertație în embriologie experimentală.

Între anii 1975 și 1978 a desfășurat stagii postdoctorale la **Universitatea din Zürich**, în laboratorul profesorului Rolf Nöthiger, beneficiind în 1976 și de

o bursă EMBO în laboratorul doamnei Madeleine Gans, la CNRS Gif-sur-Yvette. În anul 1978 a obținut prima sa poziție independentă, ca *Group Leader* la **European Molecular Biology Laboratory (EMBL)** din Heidelberg – locul în care, alături de Christiane Nüsslein-Volhard, avea să realizeze cercetările care i-au adus consacrarea internațională.

Din 1981, profesorul Wieschaus și-a legat întreaga carieră academică de **Princeton University**, parcurgând acolo, cu eleganța discretă a marilor savanți, toate treptele academice – de la asistent la profesor titular și, ulterior, la *Squibb Professor in Molecular Biology, Emeritus*, precum și *Professor of Molecular Biology, Emeritus*, la Lewis-Sigler Institute for Integrative Genomics.

II. OPERA ȘTIINȚIFICĂ ȘI IMPACTUL DESCOPERIRILOR SALE

La sfârșitul anilor 1970, într-un mic laborator din Heidelberg, Eric F. Wieschaus și Christiane Nüsslein-Volhard au pornit de la o întrebare aparent simplă, dar de o îndrăzneală conceptuală remarcabilă: *care sunt genele care construiesc un embrion?* Pentru a răspunde, au conceput și implementat la scară masivă un proiect de mutageneză sistematică pe organismul model *Drosophila melanogaster*, urmărind saturația genomică – adică identificarea, pe cât posibil, a tuturor genelor zigotice esențiale pentru organizarea timpurie a embrionului.

Cunoscut în comunitatea științifică drept *Heidelberg Screen*, acest demers a permis caracterizarea a peste 600 de mutanți și identificarea a aproximativ 120 de gene implicate în controlul dezvoltării embrionare timpurii, dintre care 15 specifice segmentării – repartizate în categoriile *gap*, *pair-rule* și *segment polarity*. A fost un act de pionierat care a inaugurat o nouă paradigmă în biologia dezvoltării: ideea că arhitectura unui organism viu poate fi citită, gena cu gena, ca o partitură riguros organizată.

Seria de articole publicate în *Nature* (1980) și în *Wilhelm Roux's Archives of Developmental Biology* (1984), precum și descoperirea genei *Krüppel*, a reprezentat o cotitură istorică pentru biologia dezvoltării. Pentru aceste contribuții fundamentale, profesorul Eric F. Wieschaus a primit, în anul

1995, **Premiul Nobel pentru Fiziologie sau Medicină**, împreună cu Edward B. Lewis și Christiane Nüsslein-Volhard, „pentru descoperirile privind controlul genetic al dezvoltării embrionare timpurii".

Valoarea acestor descoperiri a depășit cu mult cadrul organismului model studiat. Mecanismele identificate la *Drosophila* s-au dovedit a fi, cu o fidelitate remarcabilă, conservate la toate organismele multicelulare, inclusiv la om. Multe dintre genele descoperite la Heidelberg au putut fi astfel asociate cu o fracțiune semnificativă a defectelor congenitale ereditare la om și au căpătat, în deceniile următoare, un rol major în înțelegerea cancerului. Ceea ce a început drept un studiu pe musculița de oțet a devenit, prin opera lui Eric F. Wieschaus, o gramatică universală a vieții.

Activitatea sa științifică nu s-a oprit însă aici. Profesorul Wieschaus și colaboratorii săi au contribuit decisiv la elucidarea căii de semnalizare **Wnt**, arătând, printre altele, modul în care această cale modulează nivelurile și localizarea nucleară a β-*cateninei* (cunoscută la *Drosophila* sub numele de *Armadillo*), precum și rolul GSK3β și al APC în acest proces. Cercetările sale mai recente au deschis o nouă direcție, situată la întâlnirea biologiei moleculare cu fizica: studiul cantitativ, biofizic, al schimbărilor de formă celulară și al curgerilor de țesut în timpul gastrulației, precum și măsurarea precisă a gradienților de morfogeni în embrionul timpuriu – domenii în care echipa de la Princeton continuă să fie, și astăzi, în avangarda mondială.

Rezultatele științifice ale profesorului Wieschaus se reflectă în peste 200 de lucrări indexate în *Web of Science*, într-un indice Hirsch de 82 și în peste 26.000 de citări, indicatori care îl situează între cei mai influenți biologi ai timpului nostru. Dincolo de cifre, însă, opera sa rămâne un model de *eleganță conceptuală*: fiecare experiment este construit ca o întrebare bine pusă, fiecare descoperire este așezată în arhitectura mai largă a științelor vieții.

III. RECUNOAȘTERE ACADEMICĂ INTERNAȚIONALĂ

Activitatea profesorului Eric F. Wieschaus a fost recunoscută la cel mai înalt nivel, atât prin Premiul Nobel din 1995, cât și prin numeroase alte distincții, între care amintim *The Genetics Society of America Medal* (1995)

și *Mendel Medal* a Genetical Society din Marea Britanie (1999) – onoruri care subliniază, încă o dată, impactul descoperirilor sale asupra înțelegerii eredității și dezvoltării genetice.

Apartenența sa la cele mai prestigioase societăți științifice este, la rândul ei, o mărturie a autorității sale academice. Profesorul Wieschaus este membru al **National Academy of Sciences** a Statelor Unite ale Americii, membru al **American Academy of Arts and Sciences** și membru străin al **Max Planck Society** – fapt care reflectă recunoașterea sa deopotrivă în lumea științifică americană și în cea europeană.

Aceste afilieri academice, dincolo de prestigiul lor formal, confirmă valoarea universală a contribuțiilor sale și autoritatea de care se bucură în comunitatea științifică internațională, situându-l, fără exagerare, printre figurile fondatoare ale geneticii dezvoltării moderne.

IV. PROFESORUL, OMUL, MODELUL

Dincolo de strălucirea operei sale, profesorul Eric F. Wieschaus este apreciat în comunitatea internațională pentru calități rare: rigoare intelectuală, creativitate, dăruire și seriozitate în abordarea problemelor științifice, dar și o modestie autentică și o colegialitate care au devenit proverbiale. La Princeton, generații de doctoranzi și post-doctoranzi au format, în jurul laboratorului său, o adevărată școală a gândirii științifice – o școală în care întrebările sunt mai importante decât răspunsurile, iar adevărul, mai prețios decât gloria.

Această îmbinare de excelență științifică și demnitate umană este, poate, cel mai prețios atribut al unui savant. Ea face din Eric F. Wieschaus nu doar un mare cercetător, ci și un model – un model pentru tinerii care încep astăzi, în această universitate, drumul lor în știință.

V. CONCLUZII

Având în vedere contribuțiile științifice excepționale ale profesorului Eric F. Wieschaus, impactul transformator al cercetărilor sale asupra geneticii și biologiei dezvoltării, relevanța descoperirilor sale pentru înțelegerea

dezvoltării umane, a defectelor congenitale și a cancerului, precum și recunoașterea de care se bucură la cel mai înalt nivel internațional, considerând că domnia sa îndeplinește pe deplin cerințele și criteriile prevăzute de Regulamentul privind acordarea titlurilor onorifice ale Universității din București, recomandăm cu deplină convingere și cu profund respect academic acordarea titlului de ***Doctor Honoris Causa*** al **Universității din București** domnului profesor **Eric F. Wieschaus**, aducând astfel un omagiu binemeritat unui mare om de știință și unui prieten al cunoașterii – cu speranța că legătura astfel întemeiată între domnia sa și comunitatea noastră academică va îmbogăți, pentru anii ce vor veni, dialogul dintre cele două țărmuri ale științei vieții.

Vivat, crescat, floreat!

București, 4 iunie 2026

LAUDATIO
IN HONOUR OF PROFESSOR
ERIC F. WIESCHAUS

Squibb Professor in Molecular Biology, Emeritus,
Professor of Molecular Biology, Emeritus,
Lewis-Sigler Institute for Integrative Genomics, Princeton University,
Nobel Laureate in Physiology or Medicine, 1995
on the occasion of the conferral of the title of
Doctor Honoris Causa of the University of Bucharest

Distinguished Rector,
Honourable President of the Senate of the University of Bucharest,
Distinguished colleagues, esteemed guests, dear students,

There are moments in the life of a university when the academic act transcends routine and becomes a gesture of memory and of recognition. The conferral of the title of *Doctor Honoris Causa* of the University of Bucharest upon Professor **Eric F. Wieschaus**, Nobel Laureate in Physiology or Medicine in 1995, is one such moment. It is the moment in which our academic community, with its tradition of nearly two centuries, sets alongside its own name that of one of the scholars who, in the twentieth century, profoundly transformed our understanding of life itself.

I. BIOGRAPHY AND ACADEMIC FORMATION

Eric Francis Wieschaus was born on 8 June 1947 in South Bend, Indiana, in the United States of America. He completed his undergraduate studies in biology at the **University of Notre Dame** in 1969, graduating *magna cum laude*. He continued his scientific training at **Yale University**, where in 1974 he was awarded the degree of Doctor of Philosophy in biology; his dissertation was distinguished with the John Spangler Nicholas Prize for the outstanding thesis in experimental embryology.

From 1975 to 1978 he carried out postdoctoral research at the **University of Zürich**, in the laboratory of Professor Rolf Nöthiger, having held in 1976 an EMBO short-term fellowship in the laboratory of Madame Madeleine Gans at CNRS Gif-sur-Yvette. In 1978 he obtained his first independent position as *Group Leader* at the **European Molecular Biology Laboratory (EMBL)** in Heidelberg – the place where, together with Christiane Nüsslein-Volhard, he was to undertake the research that would bring him international recognition.

From 1981 onwards, Professor Wieschaus's entire academic career has been linked to **Princeton University**, where, with the quiet elegance of great scholars, he ascended every academic rank – from assistant professor to full professor and, in due course, to *Squibb Professor in Molecular Biology, Emeritus*, and *Professor of Molecular Biology, Emeritus*, at the Lewis-Sigler Institute for Integrative Genomics.

II. SCIENTIFIC WORK AND THE IMPACT OF HIS DISCOVERIES

In the late 1970s, in a small laboratory in Heidelberg, Eric F. Wieschaus and Christiane Nüsslein-Volhard began with a question deceptively simple yet conceptually audacious: *which are the genes that build an embryo?* To answer it, they conceived and carried out, on an unprecedented scale, a programme of systematic mutagenesis on the model organism *Drosophila melanogaster*, aiming for genomic saturation – that is, for the identification, as far as possible, of all zygotic genes essential to the early organization of the embryo.

Known in the scientific community as the *Heidelberg Screen*, this endeavour led to the characterization of more than 600 mutants and the identification of approximately 120 genes involved in the control of early embryonic development, fifteen of them specific to segmentation, distributed among the *gap*, *pair-rule* and *segment polarity* classes. It was a pioneering act that inaugurated a new paradigm in developmental biology – the idea that the architecture of a living organism may be read, gene by gene, as a rigorously organized score.

The series of articles published in *Nature* (1980) and in *Wilhelm Roux's Archives of Developmental Biology* (1984), as well as the discovery of the *Krüppel* gene, marked a historic turning point in developmental biology. For these foundational contributions, Professor Eric F. Wieschaus was awarded,

in 1995, the **Nobel Prize in Physiology or Medicine**, together with Edward B. Lewis and Christiane Nüsslein-Volhard, "for their discoveries concerning the genetic control of early embryonic development".

The significance of these discoveries has reached far beyond the model organism in which they were first made. The mechanisms identified in *Drosophila* have proved, with remarkable fidelity, to be conserved across all multicellular organisms, including humans. A great number of the genes uncovered at Heidelberg have since been associated with a substantial fraction of inherited human birth defects and have, in the decades that followed, come to play a major role in our understanding of cancer. What began as a study of the fruit fly has become, through the work of Eric F. Wieschaus, a universal grammar of life.

His scientific activity, however, has not stopped there. Professor Wieschaus and his collaborators have decisively contributed to the elucidation of the **Wnt** signalling pathway, showing, among other findings, how this pathway modulates the levels and the nuclear localization of *β-catenin* (known in *Drosophila* as *Armadillo*), and clarifying the role of GSK3β and APC in this process. His more recent research has opened a new field at the meeting point of molecular biology and physics: the quantitative, biophysical study of cell-shape changes and tissue flows during gastrulation, and the precise measurement of morphogen gradients in the early embryo – a field in which the Princeton group continues, to this day, to be at the forefront of international research.

Professor Wieschaus's scientific output is reflected in over 200 articles indexed in *Web of Science*, an h-index of 82 and more than 26,000 citations – figures that place him among the most influential biologists of our time. Yet beyond such indicators, his work remains above all a model of *conceptual elegance*: every experiment is built as a finely posed question, and every discovery is set within the wider architecture of the life sciences.

III. INTERNATIONAL ACADEMIC RECOGNITION

Professor Eric F. Wieschaus's work has been recognized at the very highest level, both through the Nobel Prize of 1995 and through numerous other

distinctions, among which we may mention *The Genetics Society of America Medal* (1995) and the *Mendel Medal* of the Genetical Society of the United Kingdom (1999) – honours which underscore, once again, the impact of his discoveries upon our understanding of heredity and developmental genetics.

His membership in the most prestigious scientific societies itself is a testimony to his academic authority. Professor Wieschaus is a member of the **National Academy of Sciences** of the United States, a member of the **American Academy of Arts and Sciences**, and a foreign member of the **Max Planck Society** – a recognition that reflects his standing both within the American and within the European scientific traditions.

Beyond their formal prestige, these academic affiliations confirm the universal value of his contributions and the authority he enjoys within the international scientific community, placing him without exaggeration among the founding figures of modern developmental genetics.

IV. THE TEACHER, THE MAN, THE MODEL

Beyond the brilliance of his scientific work, Professor Eric F. Wieschaus is held in deep regard by the international community for qualities that are rare in any age: intellectual rigour, creativity, dedication and seriousness in approaching scientific problems, joined to an authentic modesty and a collegiality that have become proverbial. At Princeton, generations of doctoral and postdoctoral researchers have formed, around his laboratory, a true school of scientific thought – a school in which questions matter more than answers, and truth is dearer than glory.

This union of scientific excellence and human dignity is perhaps the most precious attribute of any scholar. It is what makes Eric F. Wieschaus not only a great researcher, but also a *model* – a model for the young men and women who, today, in this university, set out on their own paths in science.

V. CONCLUSION

In view of the exceptional scientific contributions of Professor Eric F. Wieschaus, of the transformative impact of his research on genetics

and developmental biology, of the relevance of his discoveries for the understanding of human development, of congenital disorders and of cancer, and of the recognition he enjoys at the highest international level, considering that he fully meets the requirements and criteria laid down in the Regulations on the Conferral of Honorary Titles of the University of Bucharest, we recommend with full conviction and with deep academic respect the conferral of the title of ***Doctor Honoris Causa*** of the **University of Bucharest** upon Professor **Eric F. Wieschaus**, thus paying a well-deserved tribute to a great man of science and a friend of knowledge – in the hope that the bond thus established between him and our academic community will, in the years to come, enrich the dialogue between the two shores of the life sciences.

Vivat, crescat, floreat!

Bucharest, 4th June 2026

Curriculum vitae | **Eric F. Wieschaus**

Princeton University
Department of Molecular Biology
Washington Road – Lewis Thomas Lab
Princeton, NJ 08544
efw@princeton.edu

EDUCATION AND TRAINING

University of Notre Dame, Indiana B.S. (Biology) 1969
Yale University, Biology Department Ph.D (Walter Gehring) 1974
University of Zurich, Switzerland Postdoctoral training (Rolf Nöthiger) 1975

POST-TRAINING POSITIONS

1997–2019 Investigator, Howard Hughes Medical Institute
1997–2019 Adjunct Professor of Biochemistry at the University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School
1987–Present Professor, Department of Molecular Biology, Princeton University
1983–1987 Associate Professor of Biology, Princeton University
1981–1983 Assistant Professor of Biology, Princeton University
1978–1981 Group Leader, European Molecular Biology Laboratory, Heidelberg
1977 Visiting Researcher, Peter Bryant laboratory, UCIrvine
1976 EMBO short-term fellowship to the laboratory of Mme. Gans, Laboratoire de Genetique Moleculaire, C.N.R.S., Gif-sur-Yvette, France
1975–1978 Postdoctoral Fellow, Zoologisches Institut Universität Zurich, Rolf Nöthiger

HONORS, AWARDS and PROFESSIONAL RECOGNITION

2019 Elected Fellow of the American Association of Cancer Research
2018 Lifetime Achievement Award, Society for Developmental Biology
2012 Großes Verdienstkreuz mit Stern der Bundesrepublik Deutschland
2011 Orden Pour Le Merit
2007 President, Society of Developmental Biology
2006–2015 NICHHD Merit Award
2005 Wilbur Lucius Cross Medal of the Yale Graduate School Alumni Association

2003 Inducted into the NICHD Hall of Honor
1999 Mendel Medal, UK Genetical Society
1999 Elected Foreign Member, Max-Planck Society
1997 Elected Member, American Philosophical Society
1997 Elected Associate Member, European Molecular Biology Organization
1995 The Genetics Society of America Medal
1995 Nobel Prize in Physiology or Medicine
1994 Elected Member, National Academy of Sciences
1993 Elected Fellow, American Academy of Arts and Sciences
1993 Appointed Squibb Professor of Molecular Biology, Princeton University
1989–1999 NIHHD Merit Award
1974 John Spangler Niklaus Prize for the outstanding dissertation, Yale University
1969 Graduated Magna cum laude, University of Notre Dame, South Bend, Indiana

HONORARY DEGREES

Universidad Andrés Bello, Santiago, Chile
University of Zurich, Zurich, Switzerland
Rider University, Lawrenceville, New Jersey
Rutgers University, New Brunswick, New Jersey
University of Alabama, Birmingham, Alabama
Hong Kong University of Science and Technology

ADVISORY BOARDS

2010–2020 Co-Editor in Chief, WIRES Developmental Biology
2007–2012 Member, NICHD Board of Scientific Counselors
2007–Pre Member, Advisory Board, National Institute of Genetics
1998-2008 Member, Science Advisory Board, Whitehead Institute
1998-2008 Member, Science Advisory Board, Rider University
1987-1992 Scientific Advisor Council, Damon Runyon-Walter Winchell Cancer Fund

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Article | **Eric F. Wieschaus**

Mutations affecting segment number and polarity in *Drosophila*

Christiane Nüsslein-Volhard & Eric Wieschaus

European Molecular Biology Laboratory, PO Box 10.2209, 69 Heidelberg, FRG

In systematic searches for embryonic lethal mutants of Drosophila melanogaster *we have identified 15 loci which when mutated alter the segmental pattern of the larva. These loci probably represent the majority of such genes in* Drosophila. *The phenotypes of the mutant embryos indicate that the process of segmentation involves at least three levels of spatial organization: the entire egg as developmental unit, a repeat unit with the length of two segments, and the individual segment.*

THE construction of complex form from similar repeating units is a basic feature of spatial organisation in all higher animals. Very little is known for any organism about the genes involved in this process. In *Drosophila*, the metameric nature of the pattern is most obvious in the thoracic and abdominal segments of the larval epidermis and we are attempting to identify all loci required for the establishment of this pattern. The identification of these genes and the description of their phenotypes should lead to a better understanding of the general mechanisms responsible for the formation of metameric patterns.

In *Drosophila*, the anlagen for the individual segments arise as equally sized subdivisions of the blastoderm, each segment represented by a transverse strip of about three or four cell diameters[1]. A cell lineage restriction between neighbouring segments is established at or soon after this stage[2]. Two basic types of mutation have been described which change the segmental pattern of the *Drosophila* larva. Maternal effect mutations like *bicaudal* lead to a global alteration of the embryonic pattern[3]. Bicaudal embryos develop two posterior ends arranged in mirror-image symmetry, and lack head, thorax and anterior abdomen. The *bicaudal* phenotype suggests that the initial spatial organisation of the egg established during oogenesis involves a morphogen gradient that defines antero-posterior coordinates in early embryonic pattern formation[3,4]. The subdivision of the embryo into segments is thought to occur by a differential response of the zygotic genome to the maternal gradient. Homeotic mutations (for example, *bithorax*[5,6]) seem to be involved in a final step of this response process. These mutations change the identity of individual segments; for example, *Ultrabithorax* transforms the metathoracic and first abdominal segments into mesothoracic segments. However, the homeotic loci do not affect the total number, size or polarity of the segments, nor do they point to any other step which might intervene between the maternal gradient and the final pattern of segments.

We have undertaken a systematic search for mutations that affect the segmental pattern depending on the zygotic genome. We describe here mutations at 15 loci which show one of three novel types of pattern alteration: pattern duplication in each segment (segment polarity mutants; six loci), pattern deletion in alternating segments (pair-rule mutants; six loci) and deletion of a group of adjacent segments (gap mutants; three loci) (Table 1, Fig. 1).

The segmental pattern of the normal *Drosophila* larva

Figure 2 shows the cuticular pattern of a normal *Drosophila* larva shortly after hatching. The larval body is comprised of three thoracic and eight abdominal segments. Although differences are observed in different body regions, all segments have certain morphological features in common. The anterior of each segment is marked with a band of denticles, most of which point posteriorly. The posterior part of each segment is naked. The segment borders run along the anterior margins of the denticle bands[7], they have no special morphological features. The polarity of the pattern is indicated by the orientation of the dent cles and, in the abdomen, by the shape of the bands (Fig. 3). In the thoracic segments the bands are narrow with fine denticles whereas those in the abdominal segments are broader and comprised of thick pigmented denticles (for a detailed description of the cuticular pattern see ref. 1).

Segment polarity mutants: deletions in each segment

Mutants in this class have the normal number of segments. However, in each segment a defined fraction of the normal pattern is deleted and the remainder is present as a mirror-image duplication. The duplicated part is posterior to the 'normal' part and has reversed polarity (Figs 1–3).

Six such loci have been identified. Three loci, *fused*[8], *wingless* (ref. 9 and G. Struhl, personal communication) and *cubitus interruptus*[D], were previously known whereas *gooseberry*, *hedgehog* and *patch* are new (Table 1). All the mutations in this class are zygotic lethals and the phenotypes are only produced in homozygous embryos. One of the loci, *fused*, also shows a maternal effect in that a wild-type allele in the mother is sufficient to rescue the mutant phenotype of the homozygous embryos.

In all mutants except *patch* the region deleted includes the naked posterior part of the pattern and the duplication involves a substantial fraction of the anterior denticle band. In mutant larvae, the ventral side of each segment is almost entirely covered with denticles, the posterior fraction of which point anteriorly. The segment identity seems to be normal, the denticles of the abdominal segments being large and pigmented whereas those of the thorax are short and pale (Figs 1, 2). The anterior margin of the region duplicated in these mutants coincides with the segment boundary in only two cases, *fused* and *gooseberry* (Fig. 3). In *wingless* and *hedgehog* it lies posterior to the boundary, such that these larvae apparently lack all segment boundaries.

The phenotype of embryos homozygous for *patch* contrasts with that produced by the five loci described above in that the duplicated region includes some naked cuticle anterior to each denticle band. The duplicated unit thus involves structures of two adjacent segments. *Patch* larvae, despite the normal number of denticle bands, have twice the normal number of segment boundaries (Figs 1, 3).

Despite these differences, the common feature of all mutants in this class is that a defined fraction of the pattern in each segment is deleted. This deletion is associated with a mirror image duplication of the remaining part of the pattern. We suggest that these loci are involved in the specification of the basic pattern of the segmental units.

Pair-rule mutants: deletions in alternating segments

In mutants of this class homologous parts of the pattern are deleted in every other segment. Each of the six loci is characterized by its own specific pattern of deletions (Table 1, Figs 1, 4). For example, in *even-skipped* larvae, the denticle bands and adjacent naked cuticle of the pro- and metathoracic, and the 2nd, 4th, 6th and 8th abdominal segments are lacking. This results in larvae with half the normal number of denticle bands separated by enlarged regions of naked cuticle (Figs 1, 4). In *paired* larvae the apparent reduction in segment number results

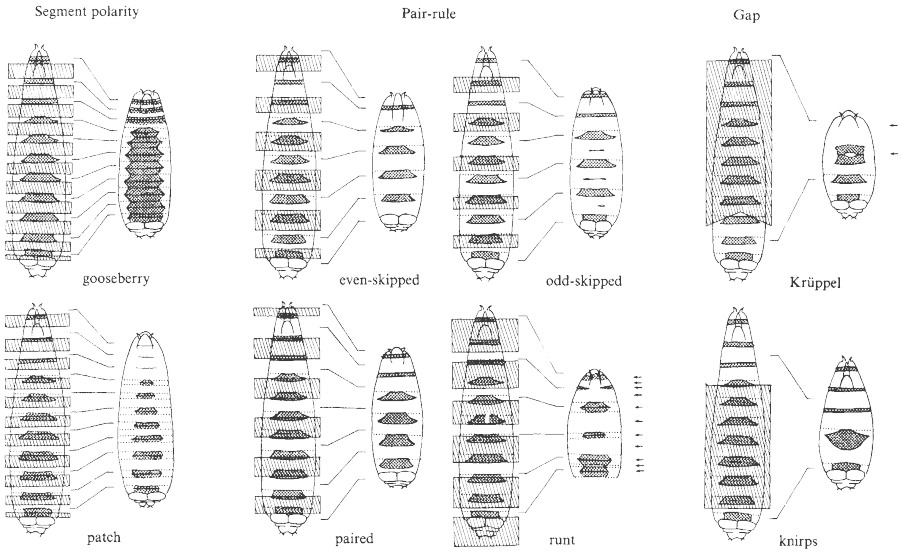


Fig. 1 Semi-schematic drawings indicating the regions deleted from the normal pattern in mutant larvae. Dotted regions indicate denticle bands, dotted lines the segmental boundaries. The regions missing in mutant larvae are indicated by the hatched bars. The transverse lines connect corresponding regions in mutant and normal larvae. Planes of polarity reversal in *runt* and *Krüppel* are indicated by the arrows. The two segment polarity loci *patch* and *gooseberry* are represented at the left. For indication of the polarity of the patterns, see Fig. 3. The patterns of *fused* and *ci*[D] (not shown) look similar to the *gooseberry* pattern, whereas in *hedgehog* and *wingless* the deleted regions are somewhat larger, cutting into the denticle bands at either side. Four pair-rule mutants are shown in the centre. The interpretation of their phenotypes is based on the study of weak as well as strong alleles, combinations with *Ubx* (see text) and, in the case of *runt*, on gynandromorphs (unpublished). They probably represent the extreme mutant condition at the respective loci. The phenotypes of all known *barrel* and *engrailed* alleles (not shown) are somewhat variable and further studies are needed to deduce the typical phenotype. At the right, the two gap loci *Krüppel* and *knirps* are shown. Both patterns represent the amorphic phenotype as observed in embryos homozygous for deficiencies of the respective loci. The only known *hunchback* allele (not shown) deletes the meso- and metathorax.

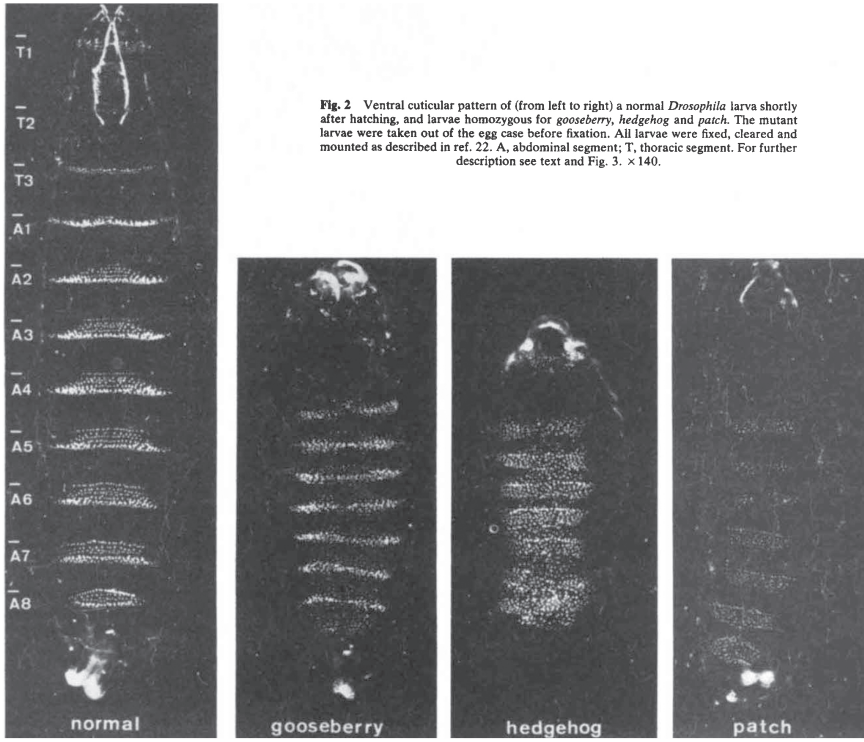


Fig. 2 Ventral cuticular pattern of (from left to right) a normal *Drosophila* larva shortly after hatching, and larvae homozygous for *gooseberry*, *hedgehog* and *patch*. The mutant larvae were taken out of the egg case before fixation. All larvae were fixed, cleared and mounted as described in ref. 22. A, abdominal segment; T, thoracic segment. For further description see text and Fig. 3. ×140.

essentially from the deletion of the naked posterior part of the odd-numbered and the anterior denticle bands of the even-numbered segments (Figs 1, 4). The double segments thus formed are composites of anterior mesothorax- and posterior metathorax, anterior first abdominal and posterior second abdominal segment, etc. The identification of the regions present or deleted in mutant larvae is based on the phenotypes produced by alleles with lower expressivity. In such embryos the deletions are in general smaller and variable in size. In a 'leaky' allele of *even-skipped*, the denticle bands of the even-numbered segments are frequently incomplete, whereas in *paired*^{2} (*prd*^{2}) the pattern deletions often involve only part of the naked cuticle of the odd-numbered segments, leading to a pairwise fusion of denticle bands (Fig. 4).

Further support for the composite nature of the segments in *prd* larvae was obtained in combinations with *Ultrabithorax* (*Ubx*), a homeotic mutation which when homozygous causes the transformation of the first abdominal segment into mesothorax[5]. In such *prd*; *Ubx* larvae, only the *denticle band* of the first double segment in the abdomen is transformed. The posterior margin of this band and the naked cuticle which follows remain abdominal in character and lack, for example, the typical mesothoracic sense organs. The composite nature of the segments in *paired* shows that the establishment of segmental identity does not require the establishment of individual segments as such.

The segmentation pattern in *prd*; *Ubx* larvae is typical of that of *paired* alone and is not affected by the *Ubx* homeotic transformation. Similarly, in *prd*;*Polycomb* larvae the naked cuticle of alternating segments is deleted just as it is in *paired* alone, even though in *Polycomb* embryos all the thoracic and abdominal segments have an 8th abdominal character[5]. These combinations, and similar ones with *even-skipped*, indicate that the observed grouping of segments in pairs depends on the position of segments within the segmental array rather than the segmental identity. These combinations thus provide evidence that mutations such as *paired* and *even-skipped* affect different processes from those altered in homeotic mutants.

Other mutants in this class show different deletion patterns. The phenotype of *odd-skipped* is similar to that of *even-skipped*. However, in this case it is the odd-numbered denticle bands that are affected. In *odd-skipped*, the deleted region is smaller and is restricted to a more posterior part of the segment than in *even-skipped* (Figs 1, 4). *Barrel* has a phenotype similar to *paired* although the pattern is often less regular (Fig. 4). *Runt*, on the X chromosome, is the only pair-rule mutant showing mirror-image duplications. *Runt* embryos have half the normal number of denticle bands, each a mirror-image duplication of the anterior part of a normal band (similar to the duplications found in *patch*). The bands in *runt* embryos, as well as the region of naked cuticle separating them, are of unequal sizes (Figs 1, 4).

To the list of pair-rule loci we have added the *engrailed*[10] locus. Lethal *engrailed* alleles[11] lead to a substantial deletion of the posterior region of even-numbered segments. In addition, the anterior margin and adjacent cuticle of each segment are

affected. Thus, the defect pattern in *engrailed* shows repeats which are spaced at both one- and two-segment intervals.

Each of the six different pair-rule loci affects a different region within a double segmental repeat. In no case does the margin of the deleted region coincide with a segment boundary. When the deleted region corresponds in size up to one entire segment (*paired*, *even-skipped*) it includes parts of two adjacent segments.

The phenotypes of the pair-rule mutants suggest that at some stage during normal development the embryo is organized in repeating units, the length of which corresponds to two segmental anlagen.

Gap mutants: one continuous stretch of segments deleted

One of the striking features of the mutations of the first two classes is that the alteration in the pattern is repeated at specific intervals along the antero-posterior axis of the embryo. No such repeated pattern is found in mutants of the third class and instead a single group of up to eight adjacent segments is deleted from the final pattern. Three loci have been identified which cause such gaps in the pattern (Table 1, Figs 1, 5). *Krüppel* (*Kr*) was originally described by Gloor[12]. Embryos homozygous for *Kr* lack thorax and anterior abdomen. The posterior-terminal region with the abdominal segments 8, 7 and 6 is normal, although probably somewhat enlarged. Anterior to the 6th abdominal segment is a plane of mirror-image symmetry followed by one further segment band with the character of a 6th segment oriented in reversed polarity. The exact position of the plane of symmetry varies and does not usually coincide with a segmental boundary. A large part of the *Krüppel* pattern is reminiscent of the pattern observed in embryos produced by the maternal-effect mutant *bicaudal*, although no maternal component is involved in the production of the *Krüppel* phenotype (in preparation).

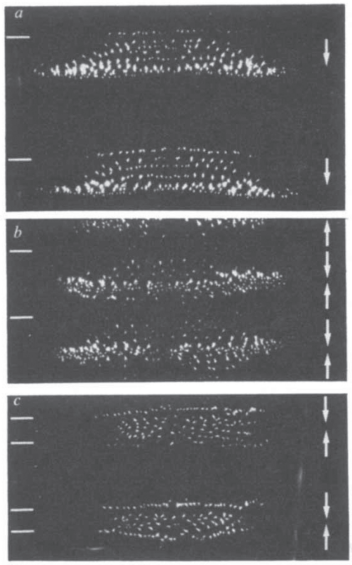


Fig. 3 Details from the ventral abdomen of a normal (*a*), a *gooseberry* (*b*), and a *patch* (*c*) larva. The positions of the segment boundaries are indicated at the left by the transverse lines. The arrows at the right indicate the polarity of the pattern as judged by the orientation of the denticles as well as the shape of the denticle bands.

Table 1 Loci affecting segmentation in *Drosophila*

Class	Locus	Map position*	No. of alleles†	Ref.
Segment-polarity	*cubitus interruptus*^{D} (*ci*^{D})	4-0	(2)	20
	wingless (*wg*)	2-30	6	9
	gooseberry (*gsb*)	2-104	1	This work
	hedgehog (*hh*)	3-90	2	This work
	fused (*fu*)‡	1-59.5	(9)	8, 20
	patch (*pat*)	2-55	8	This work
Pair-rule	*paired* (*prd*)	2-45	3	This work
	even-skipped (*eve*)	2-55	2	This work
	odd-skipped (*odd*)	2-8	2	This work
	barrel (*brr*)	3-27	2	This work
	runt (*run*)	1-65	1	This work
	engrailed (*en*)	2-62	6	11, 20
Gap	*Krüppel* (*Kr*)	2-107.6	6	12, 20
	knirps (*kni*)	3-47	5	This work
	hunchback (*hb*)	3-48	1	This work

* For the new loci (see last column) the map positions are based on recombination between the markers *S*, *Sp*, *Bl*, *cn*, *bw* for the second chromosome, and *ru*, *h*, *th*, *st*, *cu*, *sr*, *e*^{s}, *ca* for the third chromosome. For description of markers see ref. 20. The loci *runt*, *Krüppel* and *knirps* were further mapped using the breakpoints of deficiencies and duplications for the respective regions. All mutants were mapped by scoring the embryonic progeny of single recombinant males backcrossed to heterozygous females from the original mutant stocks.

† The numbers in parentheses refer to the alleles listed in Lindsley and Grell[20]. All other alleles, except the *runt* allele, three *Kr* alleles and one *knirps* allele, were isolated in a screen for embryonic lethal mutants on the second chromosome. 5,800 balanced stocks were established from individual males heterozygous for an ethyl methane sulphonate-treated *cn bw sp* chromosome using the DTS-procedure suggested by Wright[21]. 4,500 of the stocks had one or more new lethal mutations. Unhatched embryos from 2,600 putative embryonic lethal stocks were inspected for cuticular abnormalities[22]. Third chromosomal mutants discovered in the second chromosomal balanced lines were recovered after selection through individual females by balancing individual third chromosomes over TM3. Complementation tests were carried out between mutants with similar phenotypes whereby the occurrence of mutant embryos among the progeny of the crosses served as the criterion for allelism. Three new *Kr* alleles were isolated in a screen for lethals over the original *Kr* of Gloor[12], and one *knirps* allele of presumably spontaneous origin was discovered on a TM1 chromosome. The *runt* allele was isolated in a screen for X-linked lethals.

‡ *fused* is a male-rescuable maternal-effect locus[8]. Thus, the segment polarity reversal is observed in *fu*/*fu* embryos from *fu*/*fu* mothers. The progeny of *fu*/+ females show a normal embryonic pattern regardless of embryonic genotype.

In the other two loci of this class, the gap in the pattern occurs in specific morphologically defined subregions of the larval pattern, in the thorax and in the abdomen, respectively. In *hunchback*, the meso- and metathoracic segments are deleted. In embryos homozygous for *knirps*, only two rather than eight denticle bands are formed in the abdomen. The posterior-terminal region including the 8th abdominal segment seems normal whereas the anterior abdominal denticle band is considerably enlarged. The anterior margin of the denticle band is morphologically similar to the first abdominal segment but combinations with *Ubx* show that the band is a composite with more than one segmental identity.

All three loci are required for a normal segmental subdivision of one continuous body region. The lack of a repeated pattern of defects suggests that the loci are involved in processes in which position along the antero-posterior axis of the embryo is defined by unique values.

When are genes affecting segment number active?

The phenotypes described above are observed only in homozygous embryos, indicating that the loci identified by these mutations are active after fertilization and are crucial for the normal segmental organisation of the embryo. We have described the mutations in terms of their effect on the differentiated pattern. However, in many instances their effect can be observed much earlier in development. In normal embryos segmentation is first visible 1 h after the onset of gastrulation as a repeated pattern of

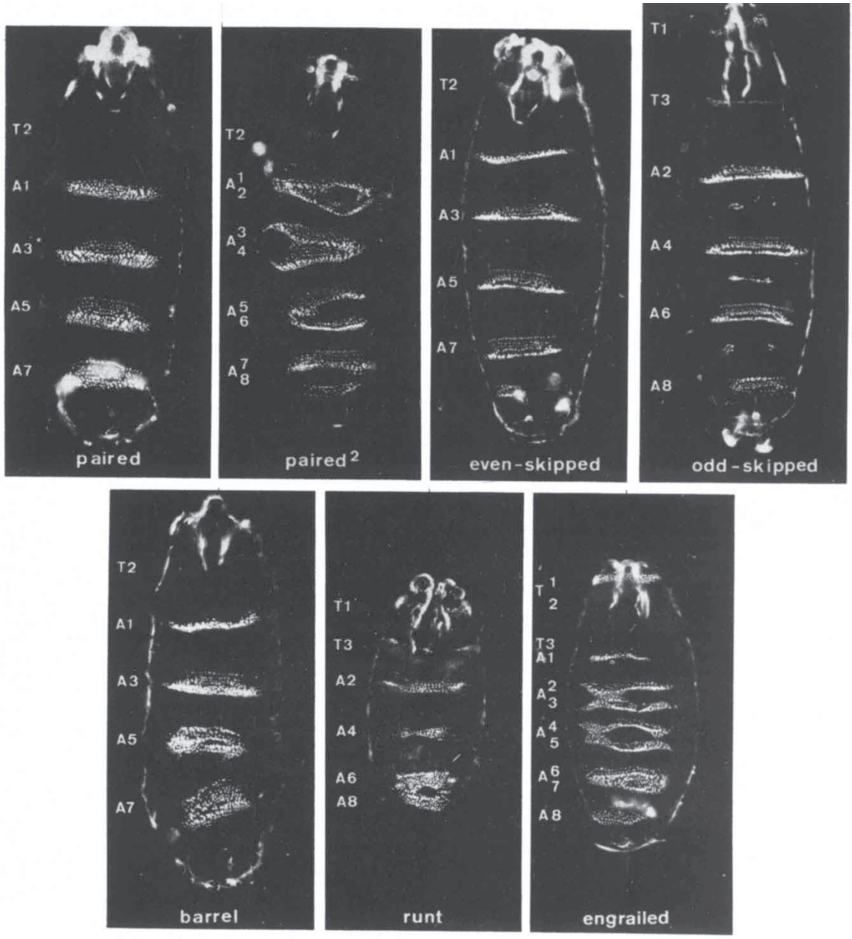


Fig. 4 Larvae homozygous for mutations at the six pair-rule loci. The segmental identity of the denticle bands is indicated at the left of each picture. A, abdominal band; T, thoracic band. For comparison with the normal pattern see Figs 1 and 2.

bulges in the ventral ectoderm (unpublished observations). In *paired* and *even-skipped* embryos the number of bulges is reduced and corresponds to the number of segments observed in the differentiated mutant embryos. *Krüppel*, *runt* and *knirps* embryos can be identified 15 min after the onset of gastrulation. All three mutations cause shorter germ bands, a phenomenon clearly related to the strong reduction in segment number observed in the differentiated larvae. Further evidence for an early activity at the *paired* locus was obtained using a temperature-sensitive allele. The extreme phenotype is only obtained when the embryo is kept at the restrictive temperature during the blastoderm stage. All these results indicate that the wild-type genes defined by the mutations are active before the end of gastrulation during normal development.

Discussion

Segmentation in *Drosophila* proceeds by the transition from a single field into a repeated pattern of homologous smaller subfields. Mutant alleles at the 15 loci we have described interfere with this process at various points. Although each locus has its own distinct phenotype, we were able to distribute the mutations in three classes. In one class only a single large subregion of the embryo is affected, whereas in mutants of the other two classes a reiteration of defects is produced with a

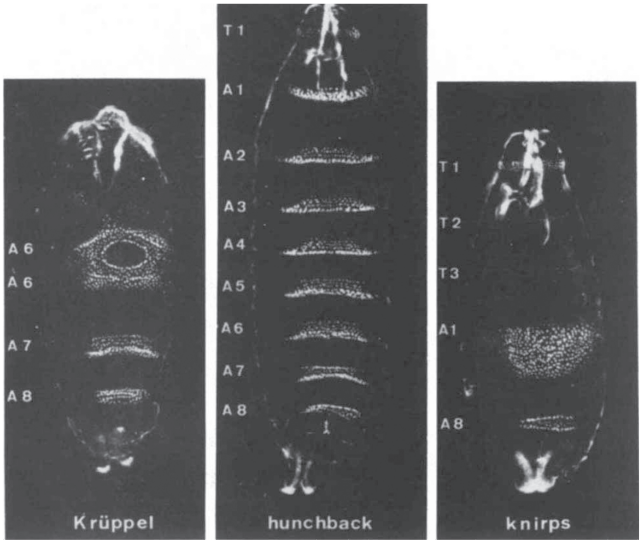


Fig. 5 Larvae homozygous for mutations at the three gap loci. A, abdominal segment; T, thoracic segment.

repeat length of one or two segments, respectively. This suggests that the process of segmentation involves three different units of spatial organization.

The organization of the egg is thought to be controlled by a monotonic gradient set up during oogenesis under the control of the maternal genome[3,4]. All the mutants we have described depend on the embryonic rather than the maternal genome. None of them alters the overall polarity of the embryo, the head always being at the anterior and the telson at the posterior end of the egg. The most dramatic alterations of the pattern are produced in the gap mutants and involve one large subregion of the egg. *Hunchback* and *knirps* affect the development of thorax and abdomen, respectively, and might be involved in the establishment of these large morphologically unique subregions of the embryo. The large mirror-image duplications found in the posterior pattern of *Krüppel* embryos are similar to those of *bicaudal*. The *bicaudal* phenotype has been interpreted as resulting from an instability in the maternal gradient[3,13], and thus *Krüppel* might be involved in the maintenance of elaboration of this gradient in the posterior egg region after fertilization.

The smallest repeat unit, the individual segment, is affected in mutants at the six segment-polarity loci. The pattern alteration consists of a mirror-image duplication of part of the normal pattern with the remainder deleted. In these mutants the deleted region corresponds in size to more than half a segment. Mutations causing smaller deletions in the segmental pattern do not lead to polarity reversals (unpublished observations). The mirror-image duplications produced by the pair-rule mutation *runt* are also associated with a deletion of more than half a repeat unit, that is, more than one segment. The tendency of partial fields containing less than half the positional values to duplicate is well described for imaginal disks in *Drosophila*[14], as well as for the larval epidermis in other insects[15,16]. On the other hand, the same types of pattern duplication are also produced in conditions which do not involve cell death and regeneration, but rather a reorganization of the positional information in the entire field[3,17]. More detailed studies of early development in mutant embryos may reveal which mechanism is responsible for the different mutant phenotypes.

Given the evidence for a homology between segments, the existence of a class of mutants affecting corresponding regions in each individual segment is perhaps not surprising. The discovery of a mutant class affecting corresponding regions in every other segment was not expected and suggests the existence at some time during development of homologous units with the size of two segmental anlagen. It is possible that the double segmental unit corresponds to transitory double segmental fields which are established early during embryogenesis and are later subdivided into individual segments. At the blastoderm stage the epidermal primordium giving rise to thorax and abdomen is only about 40 cells long[1]. An initial subdivision into double segments would avoid problems of accuracy encountered in a simultaneous establishment of segment boundaries every three to four cells. A stepwise establishment of segments implies that the borders defining double segments be made before the intervening ones. The mutant phenotypes do not definitely show which, if any, of the segment borders define a primary double segmental division in normal development. The mutant phenotypes which come closest to a pattern one would expect if the transition from the double segment to the individual segment stage were blocked are the patterns of *paired* and *even-skipped*. Both suggest the frame meso- and methathorax, 1st and 2nd, 3rd and 4th abdominal segment, etc.

It is also possible that the double segmental units are never defined by distinct borders in normal development. The existence of a double segmental homology unit may merely reflect a continuous property such as a wave with a double segmental period responsible for correct spacing of segmental boundaries (see, for example, refs 18, 19). We have not found any mutations showing a repeat unit larger than two segments. This may indicate that the subdivision of the blastoderm proceeds directly by the double segmental repeat with no larger intervening homology units. However, the failure to identify such larger units may reflect the incompleteness of our data.

Drosophila has been estimated to have about 5,000 genes and only a very small fraction of these when mutated result in a change of the segmental pattern of the larva. Some of the loci

described here were known previously but only in the case of *Krüppel* has the embryonic lethal phenotype been recognized as affecting segmentation.[12] The majority of the mutants described here have been isolated in systematic searches for mutations affecting the segmentation pattern of the *Drosophila* larva. These experiments are still incomplete. Most of the alleles on the second chromosome were isolated in one experiment which yielded an average allele frequency of four or five alleles per locus (based on 42 embryonic lethal loci). From this yield and similar calculations for the third and first chromosomes, we estimate that we have identified almost all segmentation loci on the second chromosome and about 50% each of those on the third and first chromosome. Our sample of 15 loci should therefore represent the majority of the loci affecting segmentation in the *Drosophila* genome. Thus, in *Drosophila* it would seem feasible to identify all genetic components involved in the complex process of embryonic pattern formation.

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Note added in proof: All known *barrel* alleles fail to complement *hairy*[20], suggesting that the *barrel* mutations are alleles at the *hairy* locus.

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Chemical synthesis of a polypeptide predicted from nucleotide sequence allows detection of a new retroviral gene product

J. G. Sutcliffe, T. M. Shinnick, N. Green, F.-T. Liu, H. L. Niman & R. A. Lerner

Department of Cellular and Developmental Immunology, Research Institute of Scripps Clinic, La Jolla, California 92037

We previously determined the nucleotide sequence of the 3′ end of Moloney leukaemia virus and discovered the potential coding region for an unknown protein, R. We now show that this region does encode a protein. A pentadecapeptide of R was chemically synthesized and antibodies raised against it. Antisera to the synthetic peptide recognize the R protein and the env *precursor polyprotein in infected cells. The strategy presented here should provide a general method for accessing proteins predicted by nucleotide sequences.*

THE accepted genetic structure of replication-competent murine leukaemia viruses, such as Moloney, Rauscher, Friend and AKV, includes three genes. These genes, *gag*, *pol* and *env*, are arranged, in respective order, along the single-stranded RNA genome. They are transcribed from the integrated double-stranded DNA provirus[1]. The protein products of these three genes are understood in considerable detail. The *gag* gene encodes a polyprotein of about 65 kilodaltons which is proteolytically processed to proteins, amino to carboxy terminal, of 15, 12, 30 and 10 kilodaltons, respectively[2]. These proteins are found in the core of the virion, and one, p30, has been associated with virus tropism[3]. The second gene, *pol*, is expressed as an apparent extension of the *gag* gene such that an approximately 180-kilodalton polyprotein containing both *gag* and *pol* components is observed. The polyprotein is processed to a 70-kilodalton protein which is the reverse transcriptase[4]. This enzyme is responsible for copying the single-stranded RNA genome of an infecting virus into the double-stranded DNA structure which can integrate into host DNA. The third gene, *env*, encodes a polyprotein which is glycosylated and processed into components gp70 and p15E (ref. 5). gp70 is the major envelope component and determines viral host range. It is sometimes found disulphide linked to p15E, a hydrophobic protein which may anchor gp70 to viral and cellular membranes[6]. Messenger RNA molecules have been described which can account for the expression of these three genes[7].

To understand fully the genetic structure of this class of viruses, we have been analysing their nucleotide sequences. We began our study at the 3′ end of Moloney murine leukaemia virus (Mo-MuLV) because of our particular interest in the *env* gene which was thought to be the most 3′-proximal gene. Surprisingly, we found an open reading frame which extended beyond the coding region for known viral products[8]. Even though we then had no evidence for a gene product, we provisionally named this the R-region because it is the coding region that is the furthest to the right in the genome. Here we report the detection of the R product. We chemically synthesized part of the R protein, raised antibodies to the synthetic peptide and detected immunologically cross-reactive material in infected cells.

The DNA sequence

For orientation purposes, several features of the previously reported[8] DNA sequence are presented here (Fig. 1). The DNA sequence was initially generated from an 1,108-base pair cDNA clone obtained by cloning the product of reverse transcription of

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