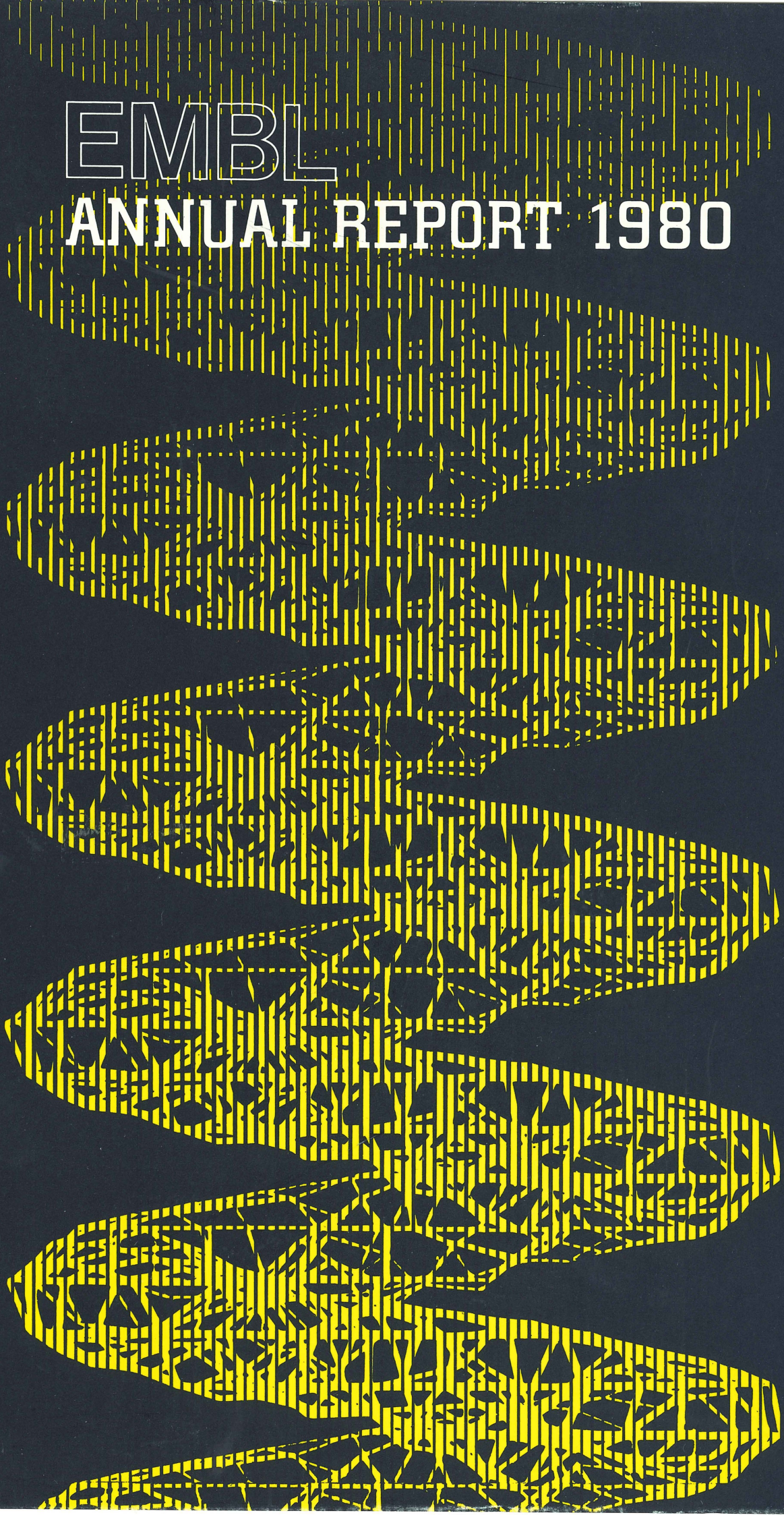
EMBL

ANNUAL REPORT 1980



cover Density distribution calculated by image reconstruction of an electron micrograph of the intracellular replication-assembly complex from Pf1 filamentous bacterial virus. Pitch is 50Å. (Photographed from an Evans & Sutherland Picture System 2 display.)

EUROPEAN MOLECULAR BIOLOGY LABORATORY

ANNUAL REPORT

1980

TABLE OF CONTENTS

1. INTRODUCTION: SOME EVENTS OF THE YEAR

1.1. Senior staff changes

The Laboratory was sad to lose three of the earliest appointed senior staff members, namely Andrew Miller, Head of the Grenoble Outstation, who has now returned to his post at the University of Oxford; Ottokar Beer who throughout the initial period had supervised the construction of the Laboratory's buildings not only in Heidelberg but also in Hamburg and Grenoble - now retired (though of course still working hard) he will still be available to the Laboratory for occasional consultation; and Richard Herzog, Head of Computing, who (together with his wife Florence who was also a member of the EMBL staff) has now taken up an appointment with the European Jet Project at Culham near Oxford.

Andrew Miller's successor as Head of the Grenoble Outstation is Bernard Jacrot, a Senior Scientist and sometime Assistant Director of the Institut Laue-Langevin. He has been given the status of Senior Scientist at the EMBL, as has Arthur Jones of the Instrumentation Division.

1.2. Teaching courses, workshops and symposia

The following courses, arranged by members of the staff in the teaching laboratories, took place in Heidelberg.

- on the electron microscopy of nucleic acids (H. Delius, 21-29 October, 8 students)

- on membrane biogenesis (H. Garoff and others, 5-16 October, 40 students).

Both the above courses were sponsored by EMBO.

The following workshops took place

- on computing and DNA sequences, organized by K. Murray at Schönau, near Heidelberg, for about 25 invited participants together with staff members (24-25 April).

- on techniques of pattern recognition and evaluation for the study of the proliferation, differentiation and movement of cells in developing tissues, and of the dynamics of intracellular constituents, organized by M. Moody for 6 invited participants (20 May).

- on applications of laser light sources and related instruments as tools for biological research, organized by L. de Maeyer for about 10 invited participants (29-30 October).

- on x-ray position-sensitive detectors and energy discriminating detectors, organized by H. Stuhrmann at the Hamburg Outstation, for about 30 invited participants together with staff members (17 to 21 November). This workshop was also sponsored by the European Science Foundation and by the Centre National de la Recherche Scientifique, Paris.

The sixth EMBO Annual Symposium entitled Molecular Biologists Look at Green Plants took place in the Laboratory from 29 September to 2 October, with upwards of 200 participants.

1.3. Visitors

Visitors during the year included Mr. Neil Macfarlane, Parliamentary Under-Secretary of State in the Department of Education and Science, United Kingdom; Mr. Hans-Hilger Haunschild, Secretary of State in the Ministry of Research and Technology, Federal Republic of Germany; Dr. G. Schmid, Chairman of the Committee for the EEC Research Programme at the European Parliament; and Dr. A. Probst, Chairman of the German Parliamentary Committee for research. A private visit was arranged for Professor G. Meyerhof of the University of Halifax, son of Professor Otto Meyerhof, the distinguished Heidelberg biochemist after whom the access road to the Laboratory is named.

1.4. Fellows

This year saw the arrival of the first predoctoral fellows in EMBL, and of the first postdoctoral fellows from the People's Republic of China.

1.5. Buildings

The main events during the year were the completion of the L4 (P4) laboratory in the Containment Facility, and its certification by the Zentrale Kommission für biologische Sicherheit; and the commencement of the construction of the building for the Outstation at Grenoble on the grounds of the ILL.

1.6. Public relations and the Press

Owing to the increasing interest taken by press, radio and television in the work of the Laboratory it has become desirable to establish a regular channel for communication with these agencies and with the public in general. Accordingly Konrad Müller of the Personnel Section in the Administration was given the (part-time) responsibilities of Public Relations and Press Officer.

During the year a number of meetings with the Press took place, and publishers and editors of daily newspapers and scientific journals from several countries visited the Laboratory. Two scientific information programs were filmed by German camera teams in the Laboratory and the Director-General and some members of the scientific staff took part in interviews for radio broadcasts.

Nine groups of schoolchildren or students from four different countries, totalling 172 participants, visited the Laboratory. The Laboratory had an information stand at the Open Day of the Internationale Gesamtschule in Heidelberg, which is attended by a number of children of staff members.

1.7. Language courses

Courses for both beginners and advanced students are now given regularly in the Laboratory in English, French and German, the tuition being given by qualified instructors from local schools. 102 members of the staff participated in the courses during 1980.

1.8. Social security

A new health insurance system was introduced at the beginning of the year, based on a budget maintained from contributions by the staff and by the Laboratory as employer instead of, as hitherto, on a contract with an insurance company. The Laboratory is the first international organization to adopt a system of this kind, which has proved itself to be a success both as regards financing and benefits, and other international organizations based in Germany have displayed considerable interest in the scheme.

2. THE SCIENTIFIC RESEARCH OF THE LABORATORY

2.1. Changes in research groups

2.1.1. The following new research groups began work in 1980

in the Division of Cell Biology

- on Molecular Genetics of Prokaryotes (Dr. Noreen Murray)

in the Division of Biological Structures

- on the DNA Sequences Data Bank (Mr. Greg Hamm)

The work of these groups is described below.

2.1.2. No research groups terminated their activities in 1980.

2.2. Division of Cell Biology

2.2.1. Structure and function of the nervous system

Members: N. Strausfeld, G. Geiger, D.R. Nässel, U. Bassemir, H. Anderson

Fellows: D. Byers, B. Mulloney*, P. Sivasubrahmanian

Visiting workers: S. Garen*, B. DeVoe*

Technical assistants: H. Seyan

Special emphasis has been on the analysis of neuronal connectivity by means of light and electron microscopy. Horseradish peroxidase has been found to pass transneuronally between certain cells. Transport of the enzyme and the number of consecutive cell assemblies filtered transneuronally has been much improved by combining horseradish peroxidase with certain substances, such as detergents and membrane mobility agents. Electron microscopy indicates that horseradish peroxidase leaves the primarily filled cells at the postsynaptic dendrites and becomes incorporated into the secondary cell at its presynaptic terminal, possibly at the site of membrane recycling of vesicles. Another haem protein, cytochrome c, is also useful as a marker of single neurons. It shows isolated cells unambiguously, since it never crosses their membranes. Earlier studies reported that cobalt ions also pass transneuronally from one cell to another. Electron microscope methods have been employed for identifying the sites of cobalt precipitates, after transneuronal staining. These are found at the postsynaptic membranes of primarily filled neurons, and in the presynaptic membrane specializations of secondarily filled neurons. There is good evidence that the passage of cobalt is *via* the synapse. Combined marking of different neurons with horseradish peroxidase and cobalt makes it possible to study the synaptic relationships of identified neurons, and to relate these to certain neuronal forms. An investigation is at

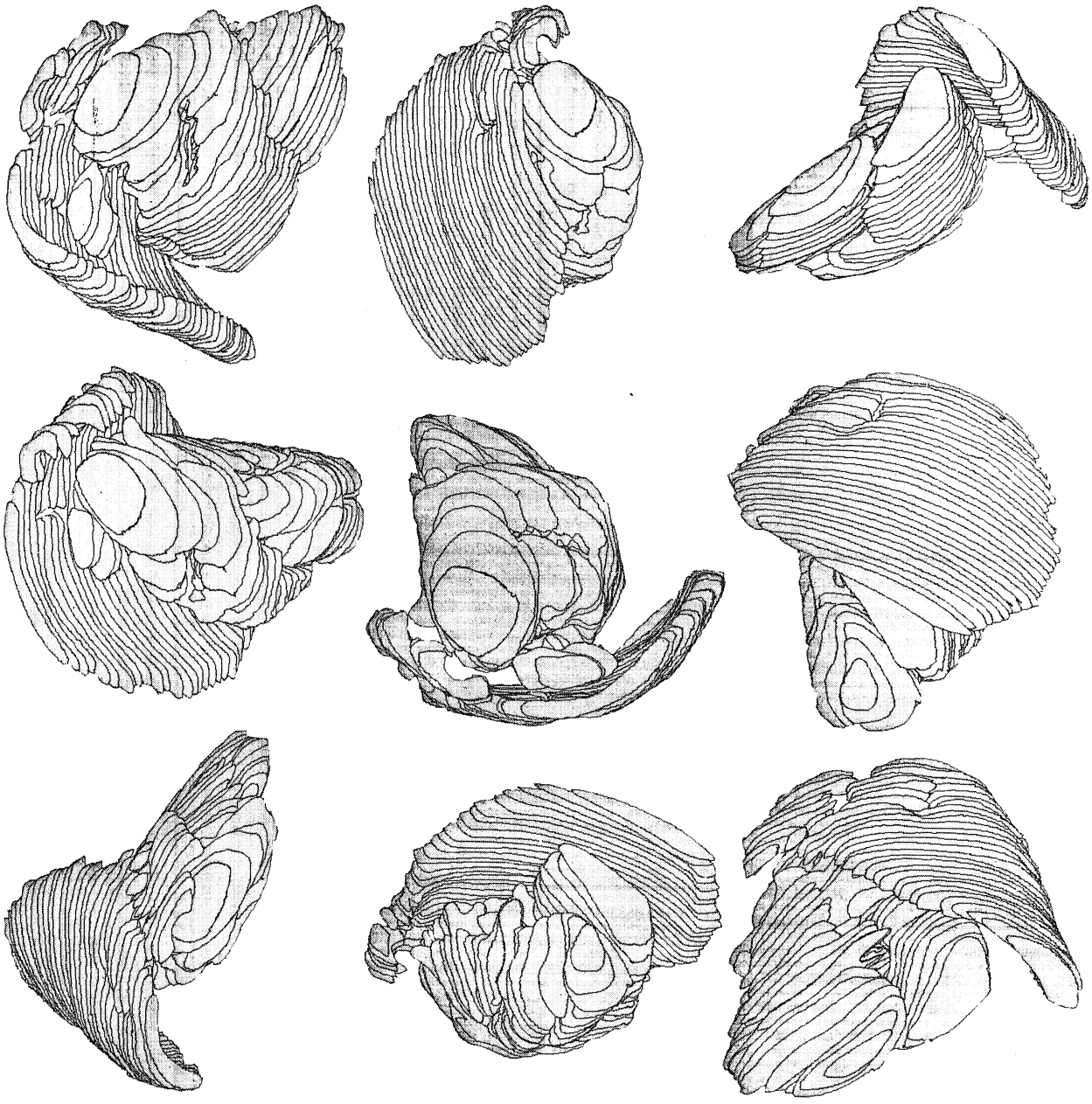


PLATE 1

Computer reconstructions from serial sections showing on top view (center image) and eight isometric views of house fly optic lobes whose structure was altered by means of laser surgery in the larva.

present being made of the system of giant descending neurons which receive inputs from visual and mechanosensory fibres. The function of these cells is also being investigated by electrophysiology, using dye-filled electrodes which in addition show up their forms and their dye coupling to other systems.

The group is also studying the effect of discrete alterations of visual neuropil, by laser ablation, on visual behaviour. Reproducible alterations which delete certain small optic lobe areas give rise to measurable abnormalities of visual behaviour. Reconstructions of altered brains are being performed with the aid of the computer graphics system devised by P.T. Speck of the Data Analysis Group (Plate 1).

Two further projects are being undertaken. One is the study of neuroanatomy in mutants of Drosophila that are deficient in olfactory learning, especially one of these that is also deficient in cyclic AMP phosphodiesterase (the dunce mutant). Another project, initiated this year, is the study of the development of sensory connections in the central nervous system of locusts.

2.2.2. Genetic analysis of embryogenesis in Drosophila melanogaster

Members: C. Nüsslein-Volhard, E. Wieschaus

Fellow: G. Jürgens

Visiting workers: F. Forquignon*, F. Minena*, G. Struhl*

Technical assistants: H. Kluding, M. Weber

In the development of higher organisms, an apparently uniform egg cell gives rise to a complex, strictly organized structure of differentiated tissues. The principles governing the correct segregation of developmental potential in a defined spatial and temporal sequence are poorly understood. We are studying this process in Drosophila, using mutants as tools to alter specific developmental decisions. By their mode of inheritance, two types of genes may be distinguished, those which are expressed during oogenesis (maternal effect mutants) and those which are expressed after fertilization indicating activity of the zygotic genome (zygotic mutants). To identify the mutations of each class, different screening procedures are required. In the past year we have completed large-scale mutagenesis screens for zygotic mutants on all three major chromosomes and have begun similar screens for maternal effect mutants.

Our results show that the number of zygotically active loci required for normal larval morphology is very small, probably not more than 2-3% of the total genome. Mutations at most of these loci have unique phenotypes, indicating that their wild-type products play specific, non-interchangeable roles during normal development. One particularly intriguing and unexpected class of mutants affects corresponding regions in every other segment. The existence of this class suggests that segmentation proceeds by the establishment of large double segmental repeat units which are later subdivided into individual segments.

2.2.3. Semliki Forest virus structure, assembly and entry into the host cell; vaccines against enveloped viruses

Members: K. Simons, H. Garoff, A. Helenius

Fellows: C. Kondor-Koch*, M. Marsh, K. Matlin, J. White

Student: H. Riedel*

Visiting workers: F. Daniel*, N. Genty*, P. Lehtovaara*, H. Söderlund*

Technical assistants: E. Bolzau, E. Kikò, A. Ohlsen*, B. Skene*, H. Virta

This group has been studying the life cycle of Semliki Forest virus in BHK-21 cells since 1970. These studies are approaching an end. Semliki Forest virus (SFV) is now one of the best characterized animal virus systems; more is known about how this virus enters its host cell and is assembled into progeny viruses than is the case for any other animal virus. These studies have not only elucidated the mechanisms of virus entry and assembly, but they have also given insights into important cellular functions. Viruses have to rely on the biochemical machinery of a cell for their reproduction. By studying viruses one is, in fact, gaining access to aspects of cell structure and function that otherwise would be difficult to investigate. SFV has turned out to be a useful probe to study membrane assembly and traffic in the animal cell, two central topics in cell biology today.

The life cycle of the virus in baby hamster kidney cells can be divided into 6 different stages: (1) entry of the virus into the cell, and introduction of its nucleic acid into the cytoplasm; (2) replication of virus RNA molecules; (3) synthesis of the virus proteins; (4) assembly of the nucleocapsid in the cytoplasm; (5) transport of the virus membrane glycoproteins from their site of synthesis in the endoplasmic reticulum through the Golgi

apparatus to the cell surface, and (6) the release of new virus particles by budding of the nucleocapsid through a segment of the plasma membrane modified to include the virus membrane glycoproteins. The only stage in the virus assembly which is still not understood is how the virus membrane glycoproteins find their way from the endoplasmic reticulum to the cell surface. This problem is being studied by G. Warren and his group (see his Report, p. 45).

SFV has not only proven a useful experimental system to study basic virus and cell functions, but the studies of the group have also resulted in a number of important spin-offs with practical applications.

1. In the elucidation of the structure of the virus membrane a considerable effort was spent on studying how different detergents solubilize the membrane and especially the amphiphilic membrane proteins. This made it possible to isolate the virus glycoproteins in non-denatured form, to prepare lipid- and detergent-free water-soluble glycoprotein complexes (protein micelles) and to reconstitute them into lipid bilayers using octylglucoside and dialysis. The methods and the basic concepts in detergent solubilization which emerged from these studies are now commonly used in membrane biochemistry.

2. The methods developed to isolate the virus glycoproteins as protein micelles turned out to be especially suitable for preparing potent subunit vaccines against enveloped viruses. It has now been shown that protein micelles are very efficient in preventing the disease caused by Semliki Forest virus in mice and by parainfluenza 3 virus in sheep (in collaboration with M. Sharp, Moredun Institute, Edinburgh, and B. Morein, State Veterinary Institute, Stockholm). Subunit vaccines against diseases caused by enveloped viruses have so far not been widely used in human and veterinary practice. The situation will probably change dramatically in the next few years with the introduction of

recombinant DNA technology to produce the needed protein antigens. The problem how to present the protein as an efficient immunogen remains. The group has shown that the protein micelle form is a promising possibility.

3. The virus entry studies showed that a number of weak bases, the so-called lysosomotropic agents, inhibit SFV infection. These compounds (chloroquine, amantadine, NH_4Cl) pass through cellular membranes in their uncharged forms. The molecules entering the lysosomes become charged and as a result they are too polar to pass back through the lysosomal membrane. They therefore accumulate and raise the intralysosomal pH above the limit necessary for induction of SFV fusion. Earlier work has shown that these compounds inhibit infection of a number of other membrane viruses, but the mechanism of inhibition had been unknown. Amantadine is, in fact, in use as an anti-viral drug against influenza virus. The recent work of the group with vesicular stomatitis virus and with influenza virus makes it likely that the inhibitory effect is due to the increase in lysosomal pH. Both of these viruses seem to use the same low pH device as SFV for entry through the lysosomes into the cytoplasm by membrane fusion. These new findings might make it possible to develop more efficient anti-viral drugs against viruses which use low pH for entry.

4. Membrane fusion has many uses in biological research. Applications include the production of hybrid cells for monoclonal antibody production and the introduction of DNA and protein into cells. Although quite successful in some cases, the available techniques are limited in their usefulness by problems of low efficiency and toxicity. The pH-dependent fusion activity of Semliki Forest virus can be used to fuse cells to each other and probably also to fuse lipid vesicles with cells. The fusion activity of Semliki Forest virus seems to be more efficient than that of Sendai virus, the classical virus fusogen. The fusion reaction is easy to control and no lysis of cells is induced. These preliminary studies indicate

that Semliki Forest virus will find application as a fusion agent.

5. Other methodological developments include methods worked out in conjunction with the sequencing of the cDNA copied from the Semliki Forest virus 26S RNA. A useful subcloning procedure was worked out mainly by H. Lehrach and A.-M. Frischauf (see their Report, p. 38). Together with W. Ansorge the gel electrophoresis step for separating the end-labelled oligonucleotides in DNA sequencing was improved (see his Report, p. 92). A simple protein sequencing method was also developed to check the amino acid sequence deduced from the DNA sequence.

2.2.4. Early events in protein secretion and membrane biogenesis

Members: B. Dobberstein, S. Kvist*

Fellows: S. Kvist*, D.I. Meyer, L.M. Roberts*

Visiting worker: F. Daniel*, D. Larhammar*

Technical assistant: M. Olsen

Selection and characterization of a cDNA clone coding for part of a mouse H-d^d major histocompatibility antigen

The major histocompatibility complex of the mouse (H-2) governs the expression of several cell surface proteins which are highly polymorphic. Among them are the H-2K, D and L transplantation antigens which are non-covalently linked to $ß_2$-microglobulin. These antigens are responsible for graft rejection and are known to be involved in the recognition of virally or chemically modified cells by cytolytic T-cells. It is hoped that a molecular analysis of these antigens and the genes coding for them will explain the polymorphism on a structural basis and also give further clues to the function of these proteins.

In collaboration with the groups of P. Kourilsky in Paris, P. Peterson in Uppsala and H. Garoff, S. Kvist has approached a structural analysis by cloning ^dDNA sequences coding for H-2 antigens. One $H\text{-}2^d$ specific cDNA clone was selected and characterized by sequence analysis. It carries a 1200 base-pair insert, comprising the non-coding region at the 3´ end and part of the coding region. The coding region extends from amino acid 133 to the carboxy-terminal end of the molecule. The availability of an H-2 specific probe will make it possible to map the polymorphism of H-2 antigens at the molecular level. Furthermore it will be possible to analyse the genes for these antigens.

A membrane protein necessary for the translocation of proteins across the membrane of the endoplasmic reticulum

The mechanism by which secretory proteins are translocated across a membrane, and plasma membrane proteins are inserted into a membrane, is unknown. The aim is to separate and isolate components involved in this process and to reassemble them into functional complexes. In doing so it is hoped to learn about the translocation process at a molecular level.

D. Meyer has characterized a membrane protein involved in translocation. This protein is part of a larger membrane protein, has a molecular weight of 60,000, is basic in character and contains an accessible sulphydryl group. In collaboration with D. Louvard, D. Meyer has raised highly specific antibodies against this protein. Using these antibodies the intact membrane form of the 60,000 dalton fragment was found to have a molecular weight of 80,000. These antibodies should allow a further functional characterization of the translocation-active protein and furthermore facilitate the search for other membrane proteins involved in protein translocation across membranes.

2.2.5. Expression and control of genes for secretory proteins in Chironomus

Members: J.-E. Edström, H. Jäckle*

Fellows: J. Cury de Almeida*, H. Sierakowska*

Students: L. Rydlander*

Visiting workers: A. Giuditta*, R. Tanguay*

Technical Assistants: K. Burvall*, C. Francke*, N. Riedel

One of the important goals in cell biology is to reach an understanding how a gene is turned on and off. Insect salivary glands with giant polytene chromosomes are particularly advantageous for studies of this problem because they offer unique possibilities for morphological identification and, in addition, because of the large size of the cells and their nuclei which makes them suitable for microdissection and as recipients for microinjected DNA and gene products. The group has obtained evidence that certain active gene loci in salivary glands of Chironomus, the so-called Balbiani rings (BR), code for giant secretory proteins. One of the BR, BR6, can be induced from a previously inactive state to become the most active gene in the cell, accounting for about one fourth of the total protein synthesis. The group is approaching the mechanism of BR6 induction from two directions - first, by following the metabolic changes after application of inducers, and second, by cloning the gene for subsequent gene control studies.

Different agents inducing BR6 all lower inorganic phosphate, an effect which turned out to be essential for BR6 induction. Subsequent metabolic steps are now being followed, including the localization of nuclear components such as newly appearing nuclear proteins, for which purpose microdissected chromosomes are used. The cloning work has been considerably facilitated by the development of a new technique (see below) which can be used for

microdissected chromosome fragments. The resulting clones could eventually be used to identify messengers and their precursors, following structural changes of the gene during induction and measuring transcriptional activity in cloned DNA injected into induced and non-induced salivary gland nuclei, etc.

A second line of the work in the group is to participate in the development of microtechniques for gene expression studies. In collaboration with the laboratories of Pirrotta and Melli a technique for the cloning of microdissected chromosome segments representing DNA in quantities down to about 10 pg has been worked out. The further improvement in sensitivity of this technique by an order of magnitude would make it suitable for a number of additional applications such as genome changes during meiosis, individual mammalian chromosomes, the Drosophila Y chromosome, etc. At present, there are no easy technical alternatives for studies of this kind. Current work shows that this goal is realistic and likely to be reached during the coming year.

2.2.6. Gene expression and its control

Members: K. Murray, A.R. Dunn

Fellows: N.C. Gough*, R. Perez Mellado, U. Reif*

Visiting workers: T. Burnett*, M. McCrae*, M. Viola*

Technical assistant: H. Krischke

Two systems are being used in studies of gene expression. One of these, the histone genes, is of interest for both the product and control of expression of the gene, and the other, the viral antigen genes, with regard to regulation of expression and involvement with host cell transformation, particularly malignant transformation.

Histone genes from sea urchins and yeast have been cloned in both bacteriophage λ and plasmid vectors and propagated in Escherichia coli. Here the objective is the production of histone in E.coli so that mutants can then be engineered which will provide opportunities to harness the approaches of biochemical genetics to the analysis of histone function. Transcription of histone genes in λ vectors has been examined extensively but translation of the mRNA produced has not been demonstrated. These studies are being extended in the construction of new recombinants where various segments of histone genes are being fused to control sequences from some bacterial genes.

Hepatitis B virus (HBV) has a small DNA genome which has been cloned in E.coli plasmid and phage vectors, and some of the viral antigen genes can be expressed in E.coli. From the nucleotide sequence of cloned HBV DNA the general organization of the viral genome has been deduced. Some of the recombinant plasmids are therefore being used as substrates for transcription with cell-free extracts of RNA polymerase II in attempts to locate sequences controlling expression. Oligomeric HBV DNA

molecules have been constructed from some rather unusual HBV DNA molecules isolated as recombinants with the E.coli plasmid pBR322 and are being put into a variety of animal cells. These and other similar experiments have as their combined objectives the productive infection of the cell with HBV, the integration of the viral genome into the host cell, and morphological transformation of the host cell, all of which will illuminate the life cycle of the virus and the general problem of gene expression and its regulation. DNA from hepatoma cell lines is being cloned in E.coli vectors (in collaboration with Prof. P.H. Hofschneider and his colleagues) for related studies of integration of viral DNA into the host genome.

For studies of neoplastic transformation of mammalian cells by DNA tumour viruses several independent lines of epithelial cells that are mutant in their thymidine kinase gene have been established from rat liver. These are being infected with cloned fragments of viral DNA, using the Herpes simplex thymidine kinase gene as a co-transforming selectable marker, in order to examine the role of viral genes in the changes that occur in animal cells with the onset of malignancy.

2.2.7. Molecular genetics of prokaryotes

Members: N.E. Murray*, G. Cesareni

Fellow: R. Lacatena

Student: G. Camilloni*

Technical assistants: J. Gough, H. Senior

This group is studying basic biological processes *via* a combination of genetic and molecular approaches. These processes include the mechanism and control of DNA replication of a small multicopy plasmid and the control and specificity of bacterial restriction and modification systems.

The approaches to an understanding of plasmid replication have been twofold. First, mutations affecting plasmid replication have identified a region outside the 600 base pair sequence (Backman *et al.*, 1978) previously shown to contain all information essential for DNA replication. Changes in this region apparently affect the copy number of the plasmid. Second, the study, *in vivo*, of transcription in the region of the origin of replication. Two promoters have been identified by fusing them to the *lacZ* structural gene so that the ß-galactosidase enzyme is now synthesized under their control. These fusions allow the isolation of mutations in the promoter regions and it is anticipated that the availability of such mutations will make it possible to deduce the relevance of these promoters to plasmid replication.

The second area of major interest is in those bacterial systems that recognize specific DNA sequences and either restrict (break) the DNA or modify (methylate) the target sequence. The organization of the 3, or possibly 4, genes determining the *E.coli* K host specificity has been deduced (Sain & Murray, 1980) and is such that it could permit the sequential expression predicted if the potential for modification of

host DNA sequences precedes that for restriction. Using operon fusions this hypothesis may be tested and, if confirmed, the mechanism of control deduced. Enterobacteriaceae, including E.coli strains, harbour a series of allelic host specificity genes each conferring the ability to recognize a different DNA sequence. The nucleotide sequences recognized by E.coli K and B are now known to be closely related and genetic tests show that the specificity is imparted by the hsdS polypeptide. Recent genetic evidence (Bullas & Colson, 1976) suggests a new specificity as the result of recombination between the specificity genes of two species of Salmonella. Comparative DNA sequences, initially of the hsdS genes, should aid the understanding of both protein-DNA interactions and evolutionary diversification.

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Sain, B. & Murray, N.E. (1980). Mol. Gen. Genet., 180, 35-46.

2.2.8. Gene organisation and expression

Member: V. Pirrotta

Fellows: T. Baldari*, C. Hadfield*, K. Kaiser, G. Scherer, A. Spena*

Student: C. Tschudi

Visiting workers: E. Calef*, P. v.d. Elsen*, N. Junakovich*, A. Viotti*

Technical assistants: D. Abildsten, J. Telford

This group is interested in the control of gene expression at the molecular level. Most of the work is now centred on Drosophila and in particular on the organization and expression of genes during embryonic development.

Different approaches have been followed to isolate and study genes involved in development. One approach has been to detect genes whose transcription is activated at specific stages of development. Using differential hybridization to mRNA sequences from different stages, clone libraries have been isolated from genomic and cDNA genes whose expression is switched on at the blastoderm stage or in the differentiation of dorsal hypoderm.

Another aproach is to isolate genes which are genetically identified, mapped and known to control developmental decisions. In collaboration with F. Scalenghe and J.E. Edström, a technique has been developed for the cloning of DNA isolated from fragments microdissected from desired regions of the Drosophila polytene chromosomes. The method now makes it possible to obtain a few hundred clones from any desired region of a few hundred kilobases on the euchromatic arms of the polytene chromosomes. It is at present being applied to clone section 3 of the X chromosome.

A ubiquitous aspect of eukaryotic molecular genetics is the presence of repetitive, disperse gene families. In the group's study of developmental gene expression, it has been found that gene families in Drosophila are regulated during development and that different families are expressed at different times. A new gene family which has been characterized is activated at the blastoderm stage, has direct terminal repeats, is found in more than 100 chromosomal sites and behaves as an insertion sequence. The finding that one of its target sites is the 5S RNA gene cluster now makes it possible to study the insertion mechanism. Similarities between this element and certain retroviruses raise interesting questions and the possibility of its use for the manipulation of genetic information.

A separate project in collaboration with A. Viotti of the Istituto Biosintesi Vegetali, CNR, Milano is aimed at the zein genes of maize. A multitude of cDNAs representing the family of zein genes has been cloned and their organization in the genome is being determined. Using corresponding genomic clones it is hoped to isolate the regulatory elements associated with the zein gene clusters.

2.2.9. Regulation of gene activity in eukaryotes

Member: M. Melli

Fellows: F. Scalenghe, E. Ullu

Students: L. Dente, V. Esposito*

Visiting workers: P. Battaglia*, E. Ginelli*, G. Spinelli*, E. Turco*

Technical assistant: K. Goldmann

This group is interested in the analysis of histone proteins in relation to their arrangement in chromatin. The problem is approached from two different angles: analysis of histone genes and their expression, and study of the genomic organization of repeated sequences in relation to the nucleosomal structure.

One of the characteristic features of eukaryotic DNA is the abundance of repeated sequences interspersed within the genome. Although nothing is known about their function several hypotheses have been proposed suggesting either a structural or a regulatory role as well as the absence of any function (Davidson & Britten, 1979; Doolittle & Sapienza, 1980; Orgel & Crick, 1980). With the development of cloning techniques it has been possible to analyse more precisely some of these sequences, in particular in Drosophila and human DNA. Drosophila DNA contains several families of sequences representing "mobile elements" which might have an important and as yet unknown regulatory role.

Approximately 3% of the human genome is accounted for by the so-called "Alu family" of sequences, which has a basic repeat of 300 base pairs present in the haploid genome at a multiplicity of 3×10^5. These sequences are transcribed and found in HnRNA and they resemble the origin of DNA replication of several viruses (Houck et al., 1979; Rubin et al., 1980; Jelinek et al., 1980).

The group has recently isolated and characterized a DNA sequence 60 base pairs long (b6) from a human DNA recombinant clone, called λHh1 (Annual Report 1979). This small fragment represents 4% of the human haploid genome and is repeated approximately 2×10^6 fold.

The comparison of the sequence of b6 with that of a number of recombinant human DNA fragments of the same family, isolated from λHh1, and with the available sequences of human recombinant DNA clones, has allowed the identification of a "consensus sequence" 30 base pairs long, which contains a small inverted repeat and seems to be highly conserved. Such a sequence is also found in adenovirus DNA. The positive cross-hybridization of b6 with mouse DNA shows that the mouse genome contains a similar highly interspersed sequence.

The conservative nature of this sequence and its ubiquity might suggest a structural role, perhaps in the organization and phasing of nucleosomes. Experiments are in progress to test this hypothesis.

Molecular hybridization with HeLa cell RNA indicates that b6 is homologous to two well-defined species of high molecular weight nuclear RNA, namely HnRNA and a small previously described cytoplasmic RNA 250 base pairs long called 7S (for review see Bishop, 1978). Characteristic of 7S RNA is its high degree of conservation in early evolutionary times. Fingerprint analyses of avian and murine, and more recently of HeLa cell, 7S RNA suggest very similar sequences (Erikson et al., 1973; Weiner, 1980). The function of this RNA species is unknown. Sequencing of a DNA copy of 7S RNA cloned into the plasmid PBR 322 is now in progress. This should clarify the relationship between the repeated fragment and the RNA structure. The availability of such a clone should permit the study of the cytological location of this small RNA and the nature of the cellular components that might interact with it.

The group has continued the analysis of human histone coding sequences, by cloning copies of HeLa cell histone mRNA into a λ phage DNA. The subcloning in a single-stranded phage of the histone gene coding sequences of the sea urchin Psammechinus miliaris has provided a convenient probe for the screening of histone recombinant molecules. The technique of selective translation has been used to confirm the coding properties of each recombinant histone DNA species. Sequencing of the histone DNA molecules is in progress.

In collaboration with G. Spinelli the group is isolating the genes coding for late blastula histone proteins from the DNA of the sea urchin Paracentrotus lividus. Late blastula histone proteins are variants and are encoded by mRNAs which diverge considerably from those of early blastula. The strategy used is, first, the cloning of cDNA copies of late blastula histone mRNA which have been isolated by cross hybridization with single histone genes of the sea urchin Psammechinus miliaris. The histone DNA recombinants are hybridized under very stringent conditions with DNA of the sea urchin Paracentrotus lividus after digestion with restriction enzymes, gel electrophoresis and Southern transfer. Once the gene is identified, it will be cloned in a λ phage after size fractionation of the DNA.

The comparison of the structure of early and late blastula genes might provide an insight into the nature of putative regulatory sequences, outside or inside the coding regions, which might be responsible for the expression of genes in different developmental stages.

The attempt to exploit the cloning technique at the nanoscale level has been successful. In collaboration with E. Turco, V. Pirrotta and J.-E. Edström a clone has been made of the DNA obtained from the dissection of approximately 10 bands of the polytene chromosomes of Drosophila melanogaster, and in particular of the region of the X-chromosome including the white and notch genes.

The cloning of this DNA (5-10 pg) has yielded 80 Drosophila DNA recombinant phages, five of which, hybridized in situ, show that the recombinant fragments seem to be randomly distributed along the same region of the X-chromosome from which they were derived. A subsequent experiment carried out with a similar amount of DNA derived from a different chromosomal fragment has given up to 500 positive recombinant phages. It is now possible to clone with relative ease genes of genetic interest for which neither the protein nor the mRNA products are known.

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2.2.10. Genetic studies of the EcoRI endonuclease and methylase

Member: M. Zabeau

Fellow: K. Breunig*

Student: L. Bougueleret

Visiting workers: J. Brooks*, J. Gielen*, D. de Martelaere*, L. van Rompuy*

Technical assistant: V. Stirling

Protein-nucleic acid interactions, and in particular those involving the recognition of defined nucleotide sequences, play a central role in the molecular biology of living cells. Despite intensive studies of several repressor-operator complexes the precise molecular basis of these interactions is still a mystery. This group is following a genetic approach to this problem by studying the site-specific EcoRI restriction endonuclease and its companion modification methylase. The aim was to devise a genetic system for isolating mutations which alter the sequence specificity of these enzymes. It is hoped that the study of these mutant enzymes will make it possible to elucidate the precise role of each of the amino acids that participate in the recognition of the target sequence.

The basic strategy was, first, to use *in vitro* recombination techniques to examine the molecular organization of the genes coding for the EcoRI restriction and modification enzymes. The isolation and characterization of recombinant plasmids carrying, and expressing, both genes or each gene separately revealed that the genes are closely linked together, and are transcribed from individual promoters. These genes were subsequently manipulated to investigate how the biological properties of the restriction and modification enzymes could be exploited to isolate enzymes with altered recognition properties. These manipulations involved (1) translocation of an active EcoRI

methylase gene into the bacterial chromosome, and (2) the construction of plasmids allowing a controlled expression of the EcoRI endonuclease. The latter was achieved by fusing the endonuclease gene to the λP_R promoter which can be experimentally switched on and off at high and low temperatures respectively in the presence of a temperature-sensitive λ repressor. Genetic analysis revealed that induction of endonuclease synthesis in strains which lack the EcoRI methylase leads to rapid cell death, presumably as a result of cleavages at non-methylated sites in the bacterial chromosome. Consequently one can now readily isolate mutations which alter the cleavage specificity of the EcoRI endonuclease by simply searching for mutations which render its activity lethal in strains that possess normal EcoRI methylase activity. Several such mutants have been isolated and are at present being studied. In the course of this investigation it was possible to demonstrate that the activity of the EcoRI endonuclease is actually subjected to a dual mode of control in the cell. First the EcoRI methylase protects the target sites for the endonuclease in the chromosome. Secondly, the endonuclease activity appears to be compartmentalized in the cell in such a way that the enzyme is prevented from acting on the cell's own chromosome and concomitantly effectively degrades incoming foreign DNA. Mutations affecting the NH_2 terminal end of the endonuclease specifically upset its balance of activity within the cell.

In collaboration with K. Stanley, G. Warren, D. Louvard and F. Winkler a new project, described on page 67, has recently been started, aimed at using recombinant DNA techniques to study the structure and organization of the clathrin gene.

2.2.11. Cloning and sequence analysis in eukaryotic molecular biology

Members: H. Lehrach, A.-M. Frischauf

Fellow: D. Leader*

Student: T. Sundt*

Visiting workers: M. Breitenbach*, M. Cipollaro*, R. Crkvenjakov*, I. Ginzburg*, N. Kecskemethy*, J.-C. Perriard*, F. Pohl*, U. Rosenberg*, K. Schäfer*

Technical assistants: R. Buckland, A. Poustka*

During the last year the group has been able to finish the project on the cloning and sequence analysis of Semliki Forest virus 26S mRNA carried out in collaboration with H. Garoff and K. Simons (Garoff et al., 1980a and Garoff et al., 1980b) and other work related to DNA sequence analysis. This has involved the development of a new sequencing strategy of general applicability (Frischauf et al., 1980), the establishment and testing of a new, rapid approach to the use of partial protein data for the verification of DNA sequences coding for proteins (Garoff, Riedel & Lehrach, in preparation), and the further development of programs for the assembly and interpretation of DNA sequence data.

These activities have made possible a further approach to problems of the regulation of gene expression, predominantly using muscle and non-muscle contractile and cytoskeletal proteins as model systems. Work in this direction has, for example, resulted in the cloning of non-muscle actin and tubulin cDNA sequences (in collaboration with I. Ginzburg, Weizmann Institute, Israel) (Ginzburg et al., 1980). Similar experiments have been carried out on the chick and mouse muscle and non-muscle genes.

The next step, the isolation of the corresponding genomic DNA sequences, is being attempted by three routes. The most commonly used procedure, involving the construction and screening of a library of genomic gene sequences in a vector, has been carried essentially to the point of completion of the library. In addition, experiments directed towards the construction of a mouse cosmid library, and the development of potentially gene-specific eukaryotic cloning vectors, have been carried out.

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2.2.12. The expression of cloned genes

Member: R. Cortese

Fellows: A. Cascino*, D.A. Melton*

Students: L. Bossi, L. Cesareni*, G. Ciliberto, F. Costanzo

Visiting workers: C. Alvino*, A. Leone*, S. Metafora*, J.D. Smith*, C. Traboni

Technical assistant: S. Ciampi

This group is interested in the study of the molecular mechanisms of gene expression. The work has been focussed on the identification of the various steps of the pathway of tRNA biosynthesis in eukaryotes, including transcription and processing. Several tRNA gene mutants have been constructed in vitro for three general purposes: (a) to modify the structure of the gene so as to interfere with, or inhibit, its capacity to function as a template for transcription, (b) to modify the gene to obtain a mutated transcriptional product, which might be altered in one or more of its multiple reactions during the process of maturation, (c) to modify the gene so as to obtain a mutated mature tRNA altered in one or more aspects of protein synthesis.

Transcriptional mutants made it possible to define three separated regions within the tRNA coding sequence that are essential for transcription. These constitute a "split" eukaryotic promoter, very different from the previously characterized prokaryotic promoters. Processing mutants made it possible to establish that all the information necessary for processing is contained within the coding sequence. Artificial creation of secondary structure outside the coding sequence results, however, in impairment of processing. Finally tRNA mutants are being characterized which are altered in their interaction with elongation factor EF-Tu and with the ribosomes.

Recently a start has been made with a project aiming at cloning genes coding for human plasma proteins. This system is interesting because (a) there are complicated mechanisms of regulation of the expression of these genes during development, (b) there are hundreds of well-characterized human "mutants" in several of these genes, and (c) a cloned gene can in principle be used to direct the synthesis of the gene product in a foreign environment (e.g. bacterial or yeast cells) so as to obtain large amounts of protein. This could be important for therapeutic purposes.

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2.3. Division of Biological Structures

2.3.1. Organization and dynamics of cytoskeletal elements

Members: B.M. Jockusch, G. Griffiths

Visiting workers: C.B. Boschek*, R.R. Friis*, G. Isenberg*, J.H. Sanger*, J.W. Sanger*

Technical assistant: K.H. Kelley

The work of this group has been concerned with several aspects of the organization of cytoskeletal elements and with intracellular transport.

Studies on the experimentally induced reorganization of microfilaments and their components in tissue culture cells have been completed. Under the influence of the drug dimethylsulphoxide, the large microfilament bundles (stress fibres) are disassembled rapidly, and their main component, actin, travels into the nucleus, where it forms actin filament bundles devoid of the other components of microfilament bundles which stay in the cytoplasm. Upon removal of the drug, actin leaves the nucleus and reassembles into stress fibres, demonstrating a rapid exchange between nuclear and cytoplasmic actin (with J.H. and J.W. Sanger and T. Kreis, E.T.H. Zürich). A detailed analysis of the breakdown of stress fibres in chicken embryo fibroblasts infected with Rous sarcoma virus mutants revealed that the observed breakdown of stress fibres is tightly coupled to the expression of a viral gene product (pp 60 kinase), is independent of protein synthesis, and, with the particular set of transformation defective, temperature sensitive mutants used, completely reversible. In the early phase of transformation microfilament components are accumulated in large surface protrusions of the plasma membrane, while in later stages the cells undergo drastic shape changes in conjunction with a complete breakdown of actin filaments

into monomeric subunits (with C.B. Boschek, R.R. Friis and H. Bauer, Univ. of Giessen). The interaction of actin filaments with two actin binding proteins, α-actinin and vinculin, has been studied in vitro. α-actinin was found to crosslink actin filaments in a strongly temperature dependent fashion, giving rise to an extensive network. Vinculin has the opposite effect on actin filaments; it induces the formation of highly ordered parallel bundles reminiscent of magnesium-induced paracrystals (with G. Isenberg, MPI Munich).

The work on clathrin-coated vesicles, which are cytoskeletal organelles involved in intracellular transport, has concentrated on the characterization of different antibodies against the major coat protein, clathrin. It has now been possible to characterize several affinity column-purified conventional antibodies with different specificities. Work is still in progress to produce a precipitating monoclonal antibody against clathrin (with H. Deschner and C. Morris).

G. Griffiths has been involved in improving the labelling of intracellular antigens (clathrin in developing spermatids, Semliki Forest virus proteins in virus-infected cells) in frozen thin sections. Two significant innovations have been the introduction of colloidal gold instead of ferritin, thereby making the marker easier to see, and an improved contrasting of membranes.

In conjunction with G. Warren's group use has been made of the technique following the path of intracellular transport of membrane proteins using Semliki Forest virus proteins as model system. In addition, a detailed morphometric analysis of this system has been made in collaboration with Prof. Weibel's group at Bern. Accurate estimates have now been made of total surface areas of membranes of endoplasmic reticulum, Golgi apparatus and plasma membrane in BHK cells. A satisfying result was that the values obtained from epon sections and from frozen sections were very similar. By combining these morphometric results with biochemical data

it is now possible to answer a number of molecular questions about the process of intracellular transport, such as the density of viral spike proteins in endoplasmic reticulum and Golgi membranes.

2.3.2. Intracellular transport of newly-synthesized plasma membrane proteins

Member: G. Warren

Fellows: B. Burke*, J. Green*, P. Quinn*

Technical assistants: R. Giovanelli*, M.-T. Sagne*

The spanning proteins in the plasma membrane are first assembled in the membrane of the endoplasmic reticulum together with proteins destined for other intracellular organelles. The plasma membrane proteins must then be separated from these other proteins during transport to the cell surface. The aim of this group is to define the nature of those cellular components responsible for this selective transport. Cells infected with Semliki Forest virus are used since viral proteins alone are being made and the cellular components responsible for transport are entirely devoted to conveying the viral membrane glycoproteins from the endoplasmic reticulum to the cell surface. During the last year it has been shown (together with G. Griffiths and B. Jockusch) that the Golgi apparatus is on this pathway. All of the Golgi stacks in an infected cell and all regions of the stack are involved in the transport of viral membrane glycoproteins.

Use has been made of a drug (monensin) that specifically blocks the transport but not the synthesis of the viral glycoproteins. The latter accumulate in Golgi vesicles covered with nucleocapsids, a feature that makes them relatively simple to isolate. What appears to be a purified sub-fraction of proximal Golgi vesicles is now being characterized.

Together with D. Louvard it has proved possible to raise antibodies that specifically stain the Golgi region in all rodent cells using indirect immunofluorescence. The antibody is directed against a protein of 145,000 daltons that is at present being characterized.

The messenger RNA coding for clathrin is being cloned and sequenced. This is reported as a separate account.

2.3.3. Mitochondrial electron transfer enzymes

Members: H. Weiss, P. Wingfield

Fellows: S. Hovmöller*, B. Karlsson*, Y. Li*

Technical assistants: B. Juchs, A. Probst*, A. Scharm, M. Slaughter

Mitochondrial oxidative phosphorylation is the principal energy-conserving process in heterotrophic eukaryotic organisms. The process is catalysed by three electron-transfer enzymes, NADH:ubiquinone reductase, ubiquinol:cytochrome c reductase and cytochrome c:O_2 oxidase, and by ATP synthase. The electron-transfer enzymes transduce oxidative energy into the energy of a trans-membrane proton gradient and the ATP synthase uses this gradient to drive the formation of ATP from ADP and inorganic phosphate. The electron-transfer enzymes and the ATP synthase account for most of the protein of the inner mitochondrial membrane.

The studies of the group have concentrated on the structure of ubiquinol:cytochrome c reductase. These have been carried out in four different ways. (1) The enzyme has been isolated as a monodisperse protein detergent complex and cleaved stepwise into subunit complexes and subunits. These preparations have been characterized biochemically and physicochemically. (2) Neutron scattering experiments have been performed with the preparations in protonated and deuterated detergents at full contrast variation from 100% H_2O to 100% D_2O (in collaboration with S. Perkins and A.R. Miller, EMBL Grenoble). (3) Two-dimensional membrane crystals have been prepared by incorporation of the preparations into phospholipid bilayers (Plate 2) and two-dimensional projected images and three-dimensional structures have been reconstructed by electron microscopy (Plate 2) (in collaboration with K. Leonard). (4) Microcrystals of the subunit complexes which protrude from the membrane (or detergent micelle) into the aqueous phase have been

PLATE 2

Electron micrograph of membrane crystals of a subunit complex from ubiquinol:cytochrome reductase containing the cytochromes b and c_1. The scale bar is 100 nm.

obtained and will be subjected to x-ray analysis if large enough crystals can be grown (in collaboration with F. Winkler). From the data obtained so far a preliminary model of this electron transfer enzyme has been proposed (Plate 4). The above studies will be continued to increase the resolution of the structure. Ultimately it is hoped that more detailed information about the structure of this electron transfer enzyme will contribute to a fuller understanding of the mechanisms of oxidative phosphorylation.

2.3.4. Biogenesis of cell surface domains as displayed by epithelial cells

Members: D. Louvard, H. Reggio

Fellow: K. Soderberg

Student: E. Coudrier

Visiting worker: C. Huet*

Technical assistants: S. Robinson, P. Webster*

This group is interested in studying the mechanisms that promote segregation of membrane components into particular organelles or areas of membrane. Such a sorting-out mechanism is required to create the specialized functional domains evident at the plasma membrane of epithelial cells. An established cell line (MDCK) forms a differentiated transporting epithelium in culture and is being used by the group as a model system to study the biogenesis of the cell surface (see Research Reports 1978 and 1979).

One working hypothesis predicts that the segregation of cell surface membrane proteins would occur inside the cell during transport between the site of synthesis and the cell surface. The Golgi complex, an organelle involved in the intracellular transport of secretory and membrane proteins, could act as a crossroad for control of this membrane traffic. Therefore a precise structural and functional analysis of this set of internal membranes is desired. Unfortunately the heterogeneity of Golgi membranes, and of internal smooth membrane in general, has made it difficult to pursue such studies using the classical approaches of subcellular fractionation and enzymatic analysis. During the past year an attempt has been made to characterize Golgi membranes using an immunological approach, defining the smooth membranes on the basis of their major antigens.

An antibody has been obtained which, when used for immunofluorescent studies, reacted with a supranuclear, tubular network within the cells. This pattern strikingly resembles the Golgi apparatus defined by the silver staining method of C. Golgi. Immunochemical studies showed that this antibody recognizes a polypeptide of molecular weight 145,000 present in purified Golgi membranes from rat liver (in collaboration with G. Warren, see his Report).

Work in progress will attempt to dissect the Golgi apparatus into structurally and functionally distinct compartments. Several monoclonal antibodies obtained recently are now being characterized for this purpose.

Small vesicles coated with an electron-dense layer of proteins are thought to participate in endocytosis and exocytosis and to act as vehicles connecting the various organelles involved in the intracellular transport of secretory and membrane proteins. A study of this protein coat and of its major constituent clathrin will therefore be necessary if an understanding is to be obtained of the various cellular functions mentioned above. A specific high affinity antibody has been obtained which can be used to localize clathrin-associated structures inside the cell, or as a probe to screen and characterize cDNA clones coding for clathrin with the eventual goal of determining the sequence of this biologically important molecule (see Report on the structure of the clathrin gene, p. 67).

Various recessive mutations have been introduced into the cell line MDCK studied in the group, including thymidine kinase deficiency and Hprt deficiency. Such mutants may prove useful for monitoring expression of DNA fragments which are inserted into the nucleus of these cells. A project to be carried out in collaboration with K. Simons' group calls for the introduction of altered cDNAs of viral membrane proteins into these cells so that the process by which surface antigens are sorted into distinct domains may be studied (see his Report). Such mutants have

already been used for the selection of somatic hybrids created with MDCK and a non-polarized cell type, namely mouse lymphocytes. It is desired to find out whether these hybrid cells, which have maintained a polar distribution of canine membrane proteins, express the murine antigens in a polar or non-polar manner.

2.3.5. Electron microscopy of nucleic acids

Members: H. Delius, B. Koller

Technical assistant: J. Clarke

Basically two methods are employed in most of the projects of this group. One is the so-called Kleinschmidt technique. Nucleic acids are spread out in a surface film of cytochrome c and their length can be accurately measured in the electron microscope. The other is adsorption of the nucleic acids to mica, in which single-stranded nucleic acids have to be complexed with a DNA-binding protein, the gene 32-protein of phage T4. This method gives more accurate measurements and higher resolution.

The main project of the group is the analysis of chloroplast DNA (cpDNA). In continuation of the work on *Vicia faba* (broad bean), cpDNA heteroduplexes have been obtained with DNA from plasmid pBK8 which contains the rRNA operon rrnD from *E.coli*. In addition to the homologies in the 16S and 23S genes, homologies can be detected in the spacer DNAs which are probably due to common tRNA sequences in *Vicia* cpDNA and the *E.coli* rrnD operon.

In collaboration with the group of T. Dyer and C. Bowman (Plant Breeding Institute, Trumpington, Cambridge) a restriction map for the cp DNA of wheat was established.

A clone containing the gene for the large subunit of ribulose biphosphate carboxylase (LS gene), the most prominent of the structural proteins of the chloroplasts, was constructed by the same group and analysed in detail by electron microscopy. The positions of the LS gene and an adjacent and not yet identified 2.4 kb gene on the same DNA fragment were measured. The *E.coli* RNA polymerase binding pattern and *in vitro* transcription revealed several distinct promoter-like positions which are located outside the structural genes. A heteroduplex

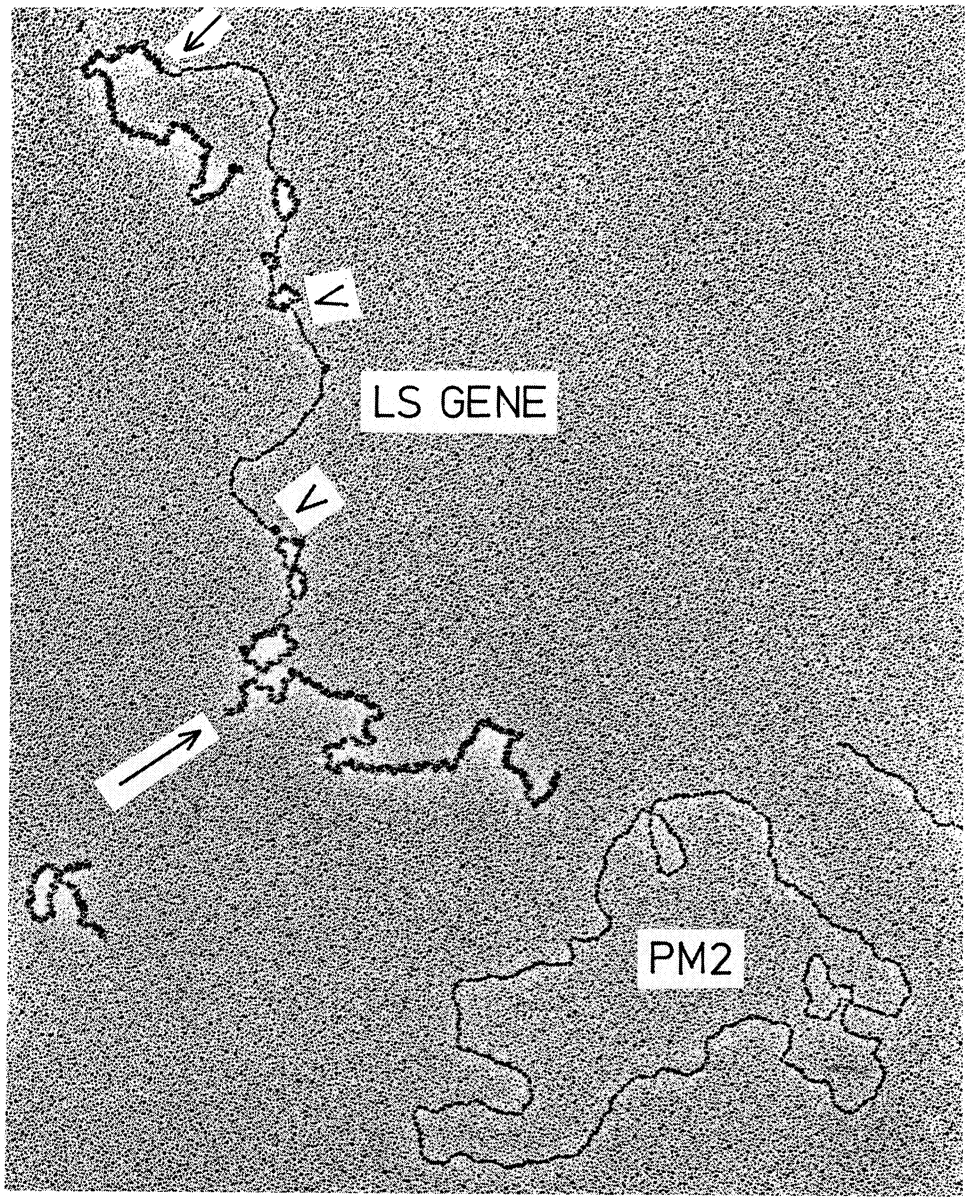


PLATE 3

A heteroduplex between DNA fragments from wheat and maize chloroplast DNA, comprising the regions of the gene for the large subunit of the ribulose biphosphate carboxylase and a second still unidentified gene. The arrows point to the ends of the maize fragment DNA. The small loops flanking the LS gene indicate mismatches between the two DNAs.

between the corresponding DNAs from wheat and from maize using the mica technique is shown in Plate 3.

Various collaborative work included:
- the analysis of recombinant λDNAs carrying histone genes from different species of sea urchin, carried out with R. Mellado (K. Murray's group). Heteroduplexes, binding of E.coli RNA polymerase and in vitro transcription complexes were studied.
- heteroduplex analysis was carried out on several clones containing DNA from Drosophila which is actively transcribed during the blastoderm stage, in collaboration with G. Scherer (of V. Pirrotta's group).
- heteroduplexes and hybrids between cloned leg-haemoglobin genes were studied in collaboration with K. Marcker and B. Borkhardt (Aarhus).
- partial denaturation maps were constructed of Tupaia adenovirus DNA (with G. Darai, Heidelberg) and of mouse adenovirus DNA (with M. Temple and E. Winnacker, Munich).

A method was developed to obtain partial denaturation maps with rather high resolution, by using a combination of formaldehyde denaturation and denaturation by gene 32-protein. This will be of interest in the comparison between experimental maps and denaturation patterns predicted from known sequences.

A new microcomputer has been installed to replace the old Wang calculator. Most of the programs for the analysis of the electron microscope data have been rewritten for the new system. All the mapping and histogram work will be much simplified by the availability of a graphic display.

2.3.6. High resolution electron microscopy group

Members: K. Leonard

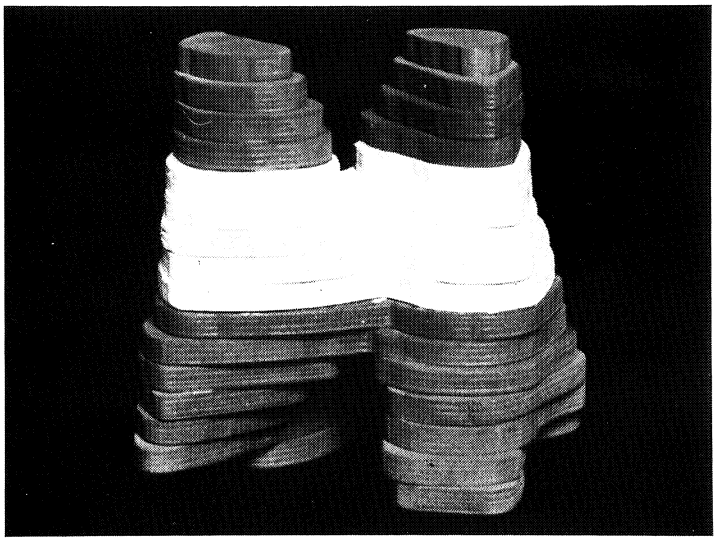
Fellows: F. Booy, S. Hovmöller*, B. Karlsson*

Visiting workers: S. Grundy*, D. Holmes*, M.A. Reedy*, M.K. Reedy*, H.G. Schramm*, I.O. Walker*

Technical assistant: T. Arad

The group is using electron microscopy combined with computer image analysis to obtain 3-dimensional structural information about biological macromolecules. Work has continued on the two-dimensional membrane crystals of cytochrome reductase from Neurospora crassa (in collaboration with the group of H. Weiss), and on similar crystals of the cytochrome b-c1 subcomplex (with S.Hovmöller and B. Karlsson). A three-dimensional model has been derived for the whole reductase molecule which is in good agreement with biochemical data for the distribution of subunits (see Plate 4) and with preliminary data for the structure of the sub-complex.

Work is also continuing with the object of improving the resolution of the membrane crystals, both by low-dose microscopy and by imaging of frozen hydrated specimens (with F. Booy).



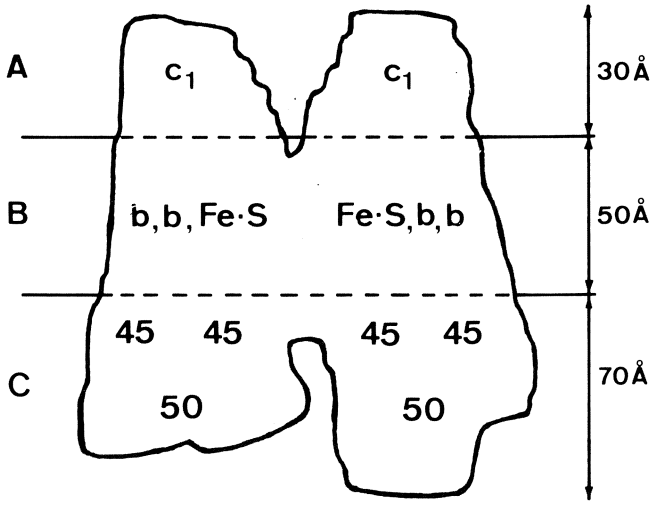


PLATE 4

a. Three-dimensional model for the cytochrome reductase molecule calculated from a tilt series of negatively-stained membrane crystals. The dimeric molecule has an asymmetric distribution of protein on opposite sides of the membrane region (here shown white).
b. Distribution of subunits found from biochemical data. The biochemical model also predicts an unequal distribution of protein on the two sides of the membrane.

2.3.7. Electron microscopy applications group

Members: J. Dubochet, R. Freeman, C.A. Walter

Fellows: J.-J. Chang*, J. Lepault

Visiting workers: A. Baudras*, B. Blasy*, J. Cartaud*, J. Christopher*, J. Escaig*, S. Grundy*, D. Holmes*, G. Moyne*, G. de Murcia*, H.G. Schramm*, M. Takahashi*

Technical assistants: J. Berriman*, A. McDowall

The main collaborations within the EMBL were on the problem of the polarity of cells (D. Louvard) and virus infection (K. Simons), on the structures of the elongation factors of E.coli (R. Leberman), of cytochrome reductase membrane crystals (K. Leonard) and of translation units from the Balbiani ring of Chironomus tentans (J.E. Edström).

The main collaborations outside the Laboratory were the continuation of the work on nucleosomes (mainly with G. Moyne, Institut Pasteur, Paris), the observation of acetylcholine receptors (J. Cartaud, IRBM, Paris) and mass measurements on various biological particles (see also the Report of K. Leonard). Promising results on the binding of the catabolic repressor protein of E.coli to DNA have recently been obtained with the group of Prof. A. Baudras in Toulouse (Plate 5).

As part of the cryo-electron microscopy project (see also Report of the E/M Development Group), the cryo-CTEM is scheduled to be installed at the EMBL in the first part of 1981. With this microscope, it should be possible to make high resolution observations of frozen-hydrated specimens before they are destroyed by the electron beam. In the meantime, the aim of the Group is to learn how to prepare and handle frozen-hydrated specimens. In particular, methods are being developed to prepare a sub-micron thin layer of frozen suspension, and to make thin sections of frozen tissues or simply

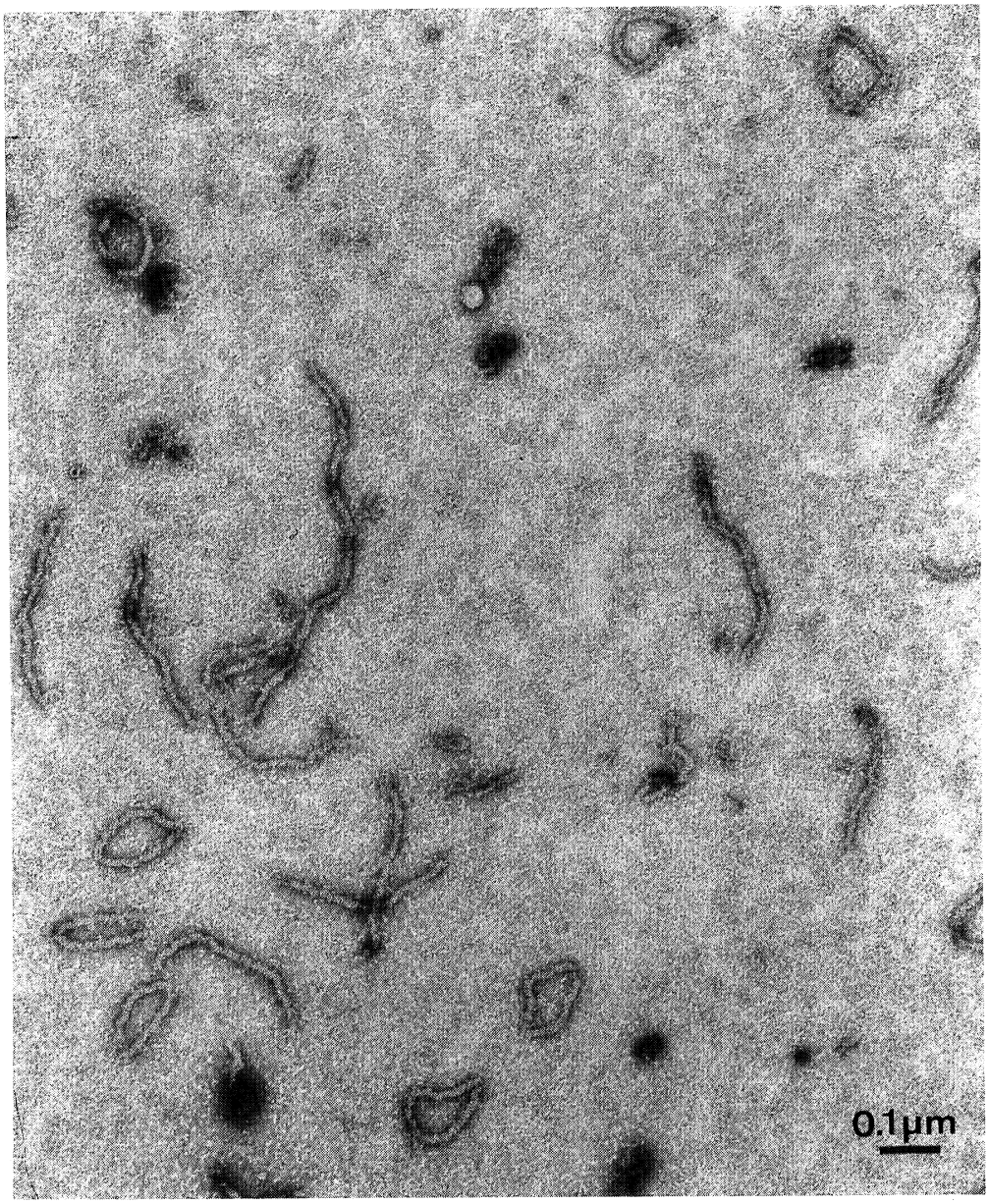


PLATE 5

Negatively-stained preparation of the fibres formed by non-specific binding of AMP receptor protein (CRP) of E.coli to DNA (in collaboration with A. Baudras, B. Blazy and M. Takahashi, Toulouse). Magnification: 100,000 times.

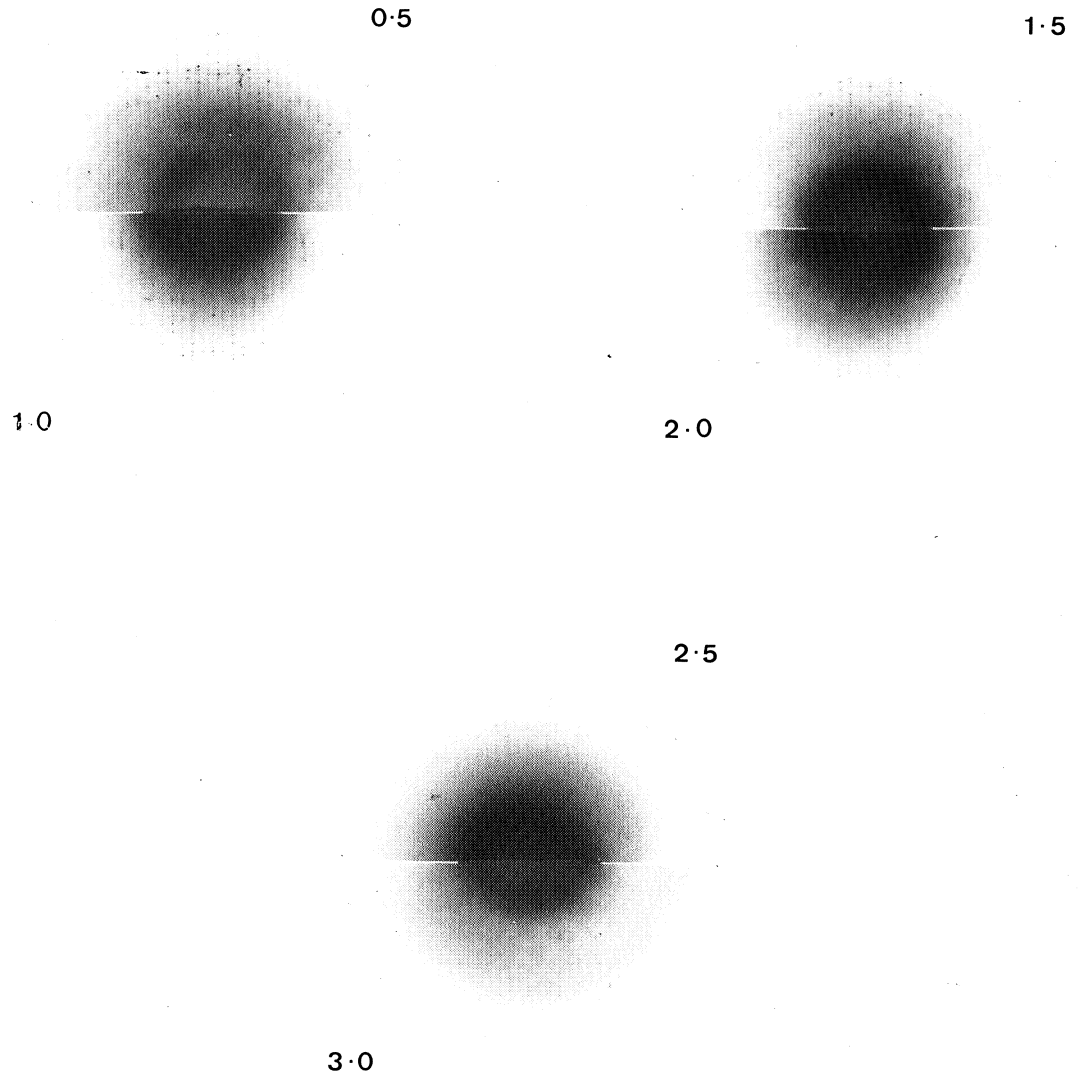


PLATE 6

Electron diffractogram of hydrated catalase crystal showing how damage increases with increasing electron dose. (The dose is given in electrons/A^2). The external ring is due to the 3.67A reflexion of cubic or hexagonal ice. Temperature: -160°C.

of ice. The manipulation and transfer of these frozen-hydrated specimens require skill, and also special equipment for which the group is grateful to the E/M Development Group. Having found satisfactory solutions to some of the preparation problems, a beginning has been made by the Group on the study of the way in which the conservation of biological structures depends on the freezing conditions, on the state of hydration, on the temperature of preparation and on electron irradiation (Plate 6).

2.3.8. Structure and assembly of filamentous bacterial viruses

Members: D.A. Marvin, D.W. Banner, G.G. Kneale, C. Nave

Fellows: W. Folkhard*, K.-O. Greulich* (part-time), W. Renner* (part-time)

Visiting Worker: S. Hamodrakas*

Technical assistants: R.S. Brown*, A.G. Fowler*

This group is working on the structure of filamentous viruses. Many important biological processes involve interactions between assemblies of macromolecules. Some examples are transport across membranes, control of DNA replication, and control of cell division. In order to understand such processes it is important to learn more about the interactions between the macromolecular structures involved. The filamentous virus system carries out many important biological functions in a simplified form, and is therefore being used as a model. The virus itself is a rod-shaped nucleoprotein consisting of a DNA core surrounded by a coat of several thousand helically arranged protein molecules. Assembly of the virus begins with the packaging of the DNA-binding assembly protein (not the same as the final coat protein) into a rod-shaped precursor particle, and with placement of the coat protein in the cell membrane. The virus is extruded through the cell membrane as the assembly protein is displaced from the DNA by the coat protein.

Samples of virus have been oriented in fibres using a strong magnetic field, a new technique that has yielded strikingly improved x-ray diffraction patterns. Data have been collected from high resolution x-ray fibre diffraction patterns of the virus and from heavy atom derivatives of the virus, and are being processed for detailed structure analysis using a suite of computer programs largely developed by the group.

Analysis of the diffraction differences between native and derivative virus gives information about the symmetry of the virus and also gives the phase information needed for detailed structure analysis. A temperature-induced transition in the virus structure has been analysed by x-ray diffraction and by solution physical chemistry. Purified samples of the complex between the viral DNA and the assembly protein have been examined using x-ray diffraction and electron microscopy. Good quality x-ray diffraction patterns have been obtained from oriented fibres of bacterial pili, the membrane-attached organelles to which the infecting virus adsorbs, and these diffraction patterns have been analysed to give a molecular model of pili.

2.3.9. Structural studies on clathrin coats and on proteins interacting with nucleic acids

Members: F.K. Winkler, K. Stanley*

Technical assistants: A. D'Arcy, H. Siegrist*, R. Brown*

This group is interested in the 3-dimensional structure of biologically important macromolecules with the aim of achieving a better understanding of their specific interactions and functions. A major goal is to grow 3-dimensional crystals of the molecules or molecular assemblies described below and to determine their structures by x-ray crystallography. As the success of crystallization attempts is very unpredictable, biochemical and other physico-chemical methods are also being used to provide relevant structural information on the molecules under study.

(a) Clathrin coats

The transport of lipid membrane between organelles in eukaryotic cells has been shown in most cases to occur by a process involving the formation of a protein coat of clathrin and associated molecules. A coated pit first appears on an invagination towards the cytoplasmic side of a membrane and then transforms into a coated vesicle by increasing its curvature and pinching off a piece of coated membrane. Subsequent disassembly of the coat allows the vesicle to fuse with another cellular membrane while the disassembled units are thought to integrate into a newly forming coated pit. The protein coat shows a netlike regular surface structure and its principal component is clathrin, a 180 kD polypeptide. *In vitro*, the coat can be reversibly dissociated into trimeric units that consist of 3 clathrin molecules and 3 polypeptide chains of smaller molecular weight ('light chains'). In the electron microscope these units appear as structures composed of three

flexible legs radiating from a centre and have been termed triskelions. During coat formation, transformation and disassembly, the triskelions must form and break contacts with themselves and with other proteins in a coordinated fashion. Much more structural information is needed to understand these processes on a molecular level. Simple questions like the spatial arrangement of clathrin and light chains in triskelions, and further that of triskelions in the coat, are under investigation by a variety of techniques. For this the group routinely isolates pure preparations of triskelions from pig brain and further separates these into clathrin and light chains. From circular dichroism data preliminary evidence has been obtained that there is a substantial difference in the amount of secondary structure between clathrin-coats and clathrin-triskelions. As more detailed structural information becomes available, there will be a need to relate this information to the amino-acid sequence of clathrin. As a major activity, therefore, the group has engaged in a collaborative project (see Report on p. 67) to clone c-DNA from clathrin messenger RNA and determine its sequence.

(b) Crystal structure analysis of proteins interacting with nucleic acids

Our knowledge about the structural details of specific protein-nucleic acid interactions is still very limited and there is a great need to determine a number of .epresentative complexes at high resolution before common patterns or rules governing these interactions can be established.

The group has prepared two DNA-interacting enzymes in amounts and purity sufficient for crystallization attempts. The two enzymes could only be obtained in sufficient quantities by means of genetic constructions leading to amplified expression of the gene products. T4 DNA ligase (overproducing strain provided by N.E. Murray) specifically

recognizes double-stranded DNA with a single strand nick and catalyses the repair of phosphodiester breaks in DNA-DNA and DNA-RNA duplexes. The other enzyme, EcoRI methylase (overproducing strain provided by M. Zabeau), recognizes the sequence (5′)pGAATTC and methylates the central adenine base. Extensive crystallization trials have not yet been successful but are being continued. Ideally, one would want to determine the structure of the enzyme with and without substrate (in this case a fragment of DNA). For this purpose a collaboration has been initiated with J. van Boom (University of Leiden, Holland) who has agreed to synthesize suitable oligonucleotide substrates in the large quantities needed. Apart from being more interesting the complexes might even be easier to crystallize if the enzymes contain flexible parts that fold up and rigidify only on substrate binding. It is also planned to study the formation of the complexes in solution by spectroscopic techniques; in particular ^{1}H and ^{31}P NMR-spectroscopy should provide valuable information on structural, kinetic and energetic aspects of the interactions responsible for recognition.

2.3.10. The structure of the clathrin gene and its sequence analysis

Members: K.Stanley, D.Louvard, G.Warren, F.Winkler, M.Zabeau

This project is being performed by collaboration between four groups in the Divisions of Cell Biology and Biological Structures. Rather than lose coherence by writing separate reports of each group's efforts, the project is presented here as one account. The aim is to obtain a sequence of the protein clathrin using recombinant DNA techniques and DNA sequencing. At the same time the number of copies of the clathrin gene will be assessed in view of the possibility that several different clathrin molecules might be used by the cell to sort membrane vesicles containing different nascent or endocytosed proteins. In the longer term it is hoped to define the precise molecular biology of clathrin and its role in membrane transport.

Clathrin is the major structural protein associated with coated vesicles, which are now recognized as an organelle involved in the transport of protein through the cell. Two distinct pathways have been recognized which involve the use of coated vesicles; one is the uptake of proteins at the plasma membrane during receptor-mediated endocytosis, and the other is the transport of newly synthesised protein from its site of synthesis at the endoplasmic reticulum (Plate 7). At both membranes clathrin molecules appear to be responsible for the process by which the membrane is pinched off to form a vesicle. Once this has been accomplished the clathrin coat dissociates again and the vesicle is free to fuse with other intracellular membranes. This process is not, however, random. During receptor-mediated endocytosis the vesicles fuse with specific intracellular sites (e.g. the lysosomes and Golgi apparatus) depending on the nature of the endocytosed protein. Similarly, secretory and membrane proteins synthesized on the rough endoplasmic reticulum are transported to a variety of different sites in a well-ordered

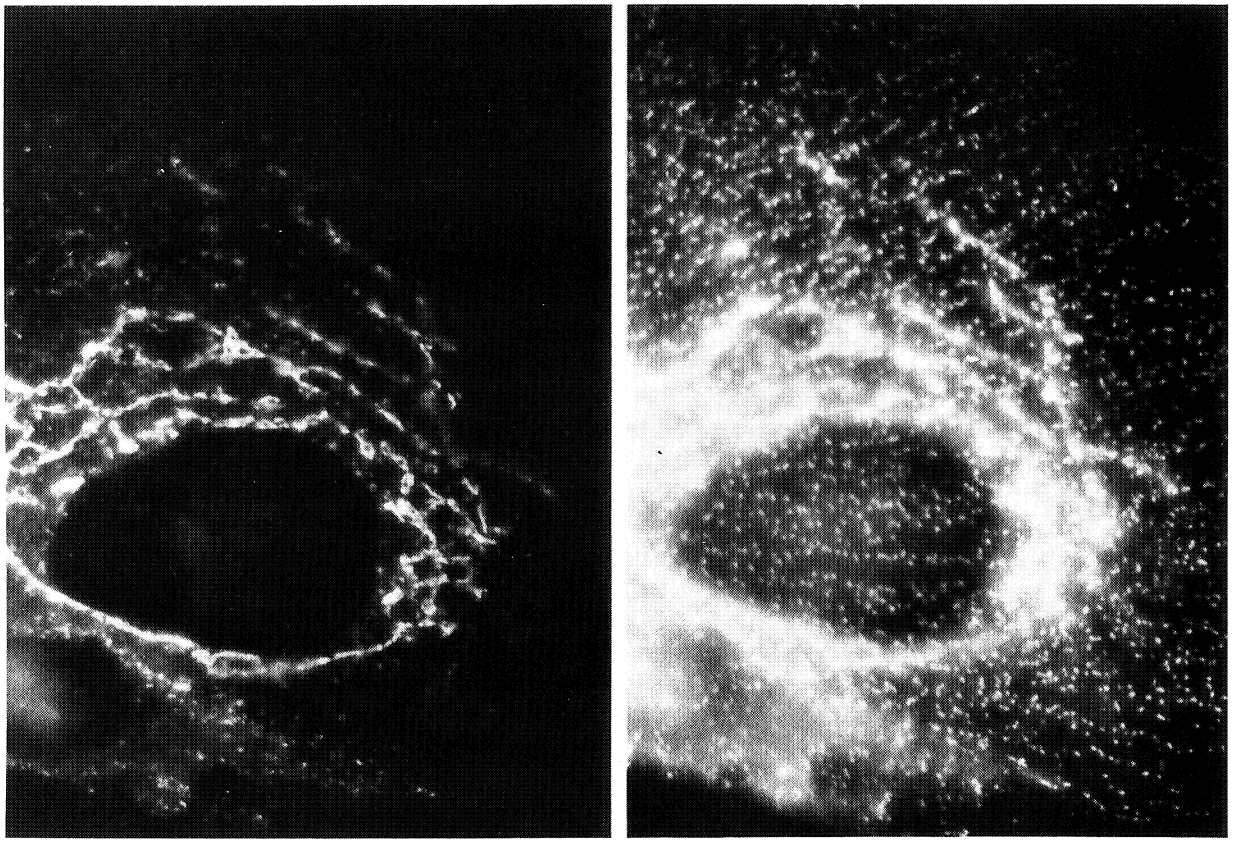


PLATE 7

Human fibroblast cells (strain WI38) were stained by indirect immunofluorescence using affinity purified rabbit anti-(pig brain) clathrin and rhodamine-labelled goat anti-rabbit IgG antibodies. This picture shows part of a single cell photographed in the fluorescence light microscope. In (a) the microscope was focused in the plane of the nucleus (the large dark body) showing the intense fluorescence associated with the Golgi apparatus, while in (b) it was focused on the cell surface showing the irregular array of coated pits formed beneath the plasma membrane.

fashion. The mechanism by which proteins are transported to specific intracellular sites in this way remains unknown. One possibility is that several different clathrin molecules exist, one specific to each route through the cell. A direct approach to this problem is to measure the number of clathrin genes expressed in a cell. This involves synthesizing double-stranded cDNA from mRNA enriched in sequences which code for clathrin, inserting this cDNA into a bacterial plasmid, and then isolating a clone of bacteria transformed with this material which contains a fragment of DNA coding for clathrin. Hybridization of this DNA with the genome of a mammalian cell should then allow the number of clathrin genes to be assessed. A second level of investigation will be to determine how many of these genes are expressed simultaneously *in vivo*.

Little is known about the structure of clathrin, how it interacts with other clathrin molecules, or how it is attached to the membranes of coated vesicles. A complete amino-acid sequence of the clathrin molecule is likely to shed some light on these problems. Since clathrin has a molecular weight of 180,000 it would take many years to determine this by protein sequencing techniques. Instead it is intended to use the rapid methods for sequencing DNA to sequence the DNA coding for clathrin, and from this to deduce the amino-acid sequence of clathrin using the genetic code and partial protein sequence information.

2.3.11. Structure of bacterial polypeptide elongation factors

Members: R. Leberman, D. Suck

Student: R. Guariguata

Technical assistant: B. Antonsson

These studies are being carried out in collaboration with the following staff of the Max-Planck-Institut für medizinische Forschung in Heidelberg

Scientists: W. Kabsch, G.E. Schulz, A. Wittinghofer

Fellow: R. Frank

Technical assistant: R. Schumann

Over the past year the group has continued its structural studies on the bacterial polypeptide elongation factors. The search for isomorphous heavy-atom derivatives required for the high resolution structure determination of the trypsin-modified EF-Tu.GDP complex was continued. A new derivative using a novel mercury complex shows great promise and an x-ray diffraction data set has been collected at the EMBL Outstation in Hamburg using synchrotron radiation. By substituting the GDP in crystals of the EF-Tu.GDP complex by ppGpp, a tetraphosphate produced in bacteria under certain starvation conditions, and using difference-Fourier methods, it has been possible to locate the nucleotide binding site of the protein.

A study of the trypsin modification of EF-Tu has revealed the composition of the material used for crystallization. The modification results in the excision of a small peptide from ala^{45}-arg^{58} and the remaining two polypeptides form a tight complex which still has many of the biological properties of the native protein.

The complex of the two elongation factors EF-Tu and EF-Ts, which constitutes half of the Qß-replicase molecule, has been crystallized. Preliminary x-ray diffraction studies have been carried out and two isomorphous heavy-atom derivatives have been found.

2.3.12. Structural basis of the allosteric control mechanism in aspartate transcarbamylase

Member: M.F. Moody

Fellow: P. Vachette

Technical assistants: A.M. Foote*, A.G. Fowler* (Instrumentation Division), P.T. Jones*

The allosteric (controllable) enzymes combine, within one molecule, the biological functions of signal reception, information transmission and effector action. Despite a great deal of work on many allosteric enzymes, the underlying stereochemical mechanisms are still a mystery. We are investigating structural aspects of the switching of the widely-studied allosteric enzyme aspartate transcarbamylase. This offers several convenient features, including a large change of shape (reflected in a large change in x-ray scattering) following the switching process. We are seeking to exploit this to study the forms present in solution under different conditions, and also to follow the kinetics of the allosteric transition, so that the time course of the structural change can eventually be compared with that of the functional activation. The state of the enzyme has been monitored by x-ray scattering, both statically and while undergoing dissociation induced by mercurials. Using an intense x-ray beam at the Hamburg outstation, the dissociation can easily be followed at 200 msec intervals. Structural aspects of the switching process are also being studied by other techniques. An EXAFS study (also at Hamburg) of the zinc ligands shows virtually no change after the enzyme is switched on, and x-ray crystallography (at both Heidelberg and Hamburg) of crystals of the isolated catalytic portion of the enzyme should make it possible to study part of the machinery in isolation.

(This work was done in collaboration with K. Bartels, H. Bartunik, J. Bordas, R. Brown, A. Gabriel, M. Koch, J. Phillips, S. Provencher and F. Winkler.)

2.3.13. Protein sequencing

Member: A. Tsugita

Fellow: K. Maeda

Students: S. Fischer*, M. Tadros*

Visiting worker: A. Dianoux*

Technical assistants: R. v.d. Broek*, J.J. Scheffler, M. Roche*

Work has continued on the development of methods for sequencing insoluble proteins, and on the determination of such sequences. It was shown that the time for complete hydrolysis could be shortened by the addition of organic acid and by raising the temperature; amino-acid recoveries were comparable to those achieved by conventional methods, and the results were more favourable for hydrophobic proteins. A method was established that gives complete hydrolysis in 25 min (Tsugita & Scheffler, 1981). A technique for partial hydrolysis, using organic acid and specific for hydrophobic amino acids, was also studied.

Projects during the year included:

- completion of the sequence of subunit VI of yeast cytochrome c oxidase, containing 108 residues; there was 28% homology with subunit V of the bovine enzyme, and haem a was absent from both subunits (Gregor & Tsugita, 1981);

- completion of the sequence of the C-terminal domain of the helix-destabilizing protein gP32 of phage T4, containing 51 residues; it is composed of clusters of aspartyl and seryl residues, and its removal leads to a greatly increased helix-destabilizing potential, to an apparent increase in affinity for single- and double-stranded DNA, and to loss of affinity for DNA polymerase and RNA-priming proteins (with J. Hosoda and I. Kubota; Hosoda *et al.*, 1980 a & b, Kubota *et al.*, 1981).

- sequence studies of the regulatory subunit of E.coli aspartyl transcarbamylase (with M.F. Moody);

- sequence studies of the ATPase inhibitor IF1 of beef heart mitochondria (with A. Dianoux, Centre d'Etudes Nucléaires, Grenoble);

- the use of the lipoprotein of the outer membrane of P. mirabilis as a model protein for the development of techniques (with R. Plapp, University of Kaiserslautern);

- preliminary studies of cell-surface glycoproteins in connection with studies of membrane adhesion in Polysphondylium pallidium (with G. Gerisch, MPI Martinsried, Munich; see Bozzaro et al., 1981);

- studies of three isomers of spinach chloroplast thioredoxin (with P. Schürmann, University of Neuchâtel; see Schürmann et al., 1981);

- preparation of metal derivatives of filamentous virus Pf1 for x-ray fibre diffraction analysis (with D.A. Marvin, see Nave et al., 1981).

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2.3.14. Nucleotide sequence data group

Member: G. Hamm*

Following the EMBL Workshop on "Computing and DNA Sequences", held in April, 1980, the need was apparent for EMBL to pursue research and development in these areas. A group for this purpose was started in October with the following goals:

1. to make available, both to EMBL staff and to the European research community, a library of known nucleic acid sequences in computer-readable form;

2. to pursue research in the application of computers to acquisition, storage, analysis, and interpretation of sequence data; and

3. to provide other groups at EMBL with computer tools for research involving nucleotide sequence information.

Work since October has concentrated on planning in the first and third areas, and on discussions with similar groups elsewhere in Europe and in the United States. Plans for 1981 include implementation of an initial library capability and the installation of apparatus for computer-assisted reading of nucleotide sequence gel autoradiograms.

2.4. Division of Instrumentation

2.4.1. Introduction

The Instrumentation Division encompasses, on the one hand, a number of technical support services for development, manufacturing and maintenance of scientific instruments, for the production of graphic and photographic artwork and for the operation of computer facilities; on the other hand, it consists of research groups actively involved in developing and investigating new tools, technologies, physical methods and instruments to support biological research in its aim to understand the molecular foundations of biological complexity.

Major areas of activity of the Instrumentation Division are:

- the development of low-temperature techniques in electron microscopy, including the development of a CRYOTEM and a CRYOSTEM, equipped with superconducting magnetic lenses and specimen stages cooled to liquid helium temperatures.

- computer analysis of electron microscope images, including on-line computer data-acquisition from a STEM, development of image data-processing programs and mathematical algorithms for structural analysis from electron micrographs.

- development of numerical methods and programs with a wide range of applicability for the quantitative analysis of experimental data. The programs are transportable to other computers and available for other laboratories.

- interactive computer graphics with applications in x-ray crystallography and molecular modelling.

- hardware and system software development to support the activities in computer applications.

- development of instruments for the application of synchrotron radiation in biological research. This includes the development of one-dimensional and two-dimensional x-ray detectors and their data-acquisition systems, support to the Hamburg Outstation in the design and construction of beam-lines and related x-ray optical equipment, development of instruments for stopped-flow time-resolved x-ray diffraction experiments at the DORIS storage ring in Hamburg.

- development of optical instruments using a picosecond visible and UV light source and the investigation of applications in the study of dynamic biological phenomena. A confocal optical scanning microscope is being developed to enable the application of new optical techniques such as fluorescence depolarization also on the microscopic (cellular) scale.

- developments and improvements to existing techniques in DNA and protein gel-electrophoresis, especially for DNA-sequence determination.

- development of new tools, methods and approaches to handle, treat, separate or purify biological materials, organelles or cells, to introduce materials into cells by microinjection and to improve various laboratory techniques by automation or computer data acquisition.

The Instrumentation Division supports the activities of the other two Divisions and of the Outstations by continuing technical assistance from its technical bureau, manufacturing and maintenance workshops, photographic and graphic artwork department, as well as by dedicated scientific staff personnel participating in biological projects that require special engineering, computer science or mathematical efforts. Collaboration with and consultation of a number of laboratories in several of the

Member States is taking place on the scientific as well as on the technical level.

With respect to its long term scientific projects the Division of Instrumentation is being advised by the Instrumentation Policy Planning Committee, consisting of a small group of regular members from Member States and elsewhere, a few members from the staff of the laboratory and a larger group of corresponding members. In the course of 1980 the laser application project was the only new activity that was started. Two other research groups with new activities were prepared to start in the next year.

2.4.2. Electron microscope development

Members: A.V. Jones, J.-C. Homo, B.M. Unitt

Technical assistants: C. Eavis*, H.J. Elema, P. Labouesse*, N. Webster

The main activity of the electron microscopy development group continues to be the design and construction of the two cryo-microscopes (see Annual Report, 1979). The cryo-objective lens from the Siemens Research Laboratory is in an advanced stage of construction and delivery is expected in April or May 1981. The Zeiss EM10 to which it will be fitted is at present being modified to minimize the post-delivery constructional work.

The cryo-STEM development continues on schedule. A large number of the basic electronic modules are complete and are at the present time being assembled into completed units. Stage 1 of the optical column (excluding the cryo-lens and detection systems) is nearing completion. System tests are not expected to begin before the latter part of 1981 because of the priority being given to the cryo-TEM at this stage of development.

2.4.3. Data analysis group

Members: S.W. Provencher, R.K. Bryan*, V.G. Dovi, P.T. Speck, R.H. Vogel

Students: J. Glöckner, G.H. Hamm*, S.M. Stier*

Visiting workers: H. Camerer*, E.A. Jonckheere*, H.-J. Wagner*

This group is mainly engaged in the development of methods for biological data analysis and, whenever possible, the implementation of these in fully documented and portable computer programs that can also be easily used outside the EMBL.

The Fortran package for linear data inversion problems is being distributed. It also contains "applications packages", which are sets of modules that can be inserted to specialize to a particular application. There are applications packages for the estimation of globular protein secondary structure from circular dichroism, the analysis of polydispersity with dynamic laser light scattering, and the inversion of Laplace transforms, of equatorial fibre diffraction data, and of low-angle scattering data. The user can also easily implement his own applications package by modifying small well-documented modules. In addition to ongoing applications mentioned previously, this package was used to study methods for characterizing neurons from dynamic electrical measurements (with H. Camerer, Tübingen), for estimating the radial position of heavy atoms in derivatives from equatorial fibre diffraction (with D. Marvin's group), and for estimating secondary structure from CD spectra of ribosomal proteins (with the groups of H.G. Wittmann, Berlin, and M. Daune, Strasbourg) and clathrin systems (with F. Winkler).

Although this package is very widely applicable, it becomes impractical for problems that are very large or nonlinear. The group has begun investigating general methods for the estimation

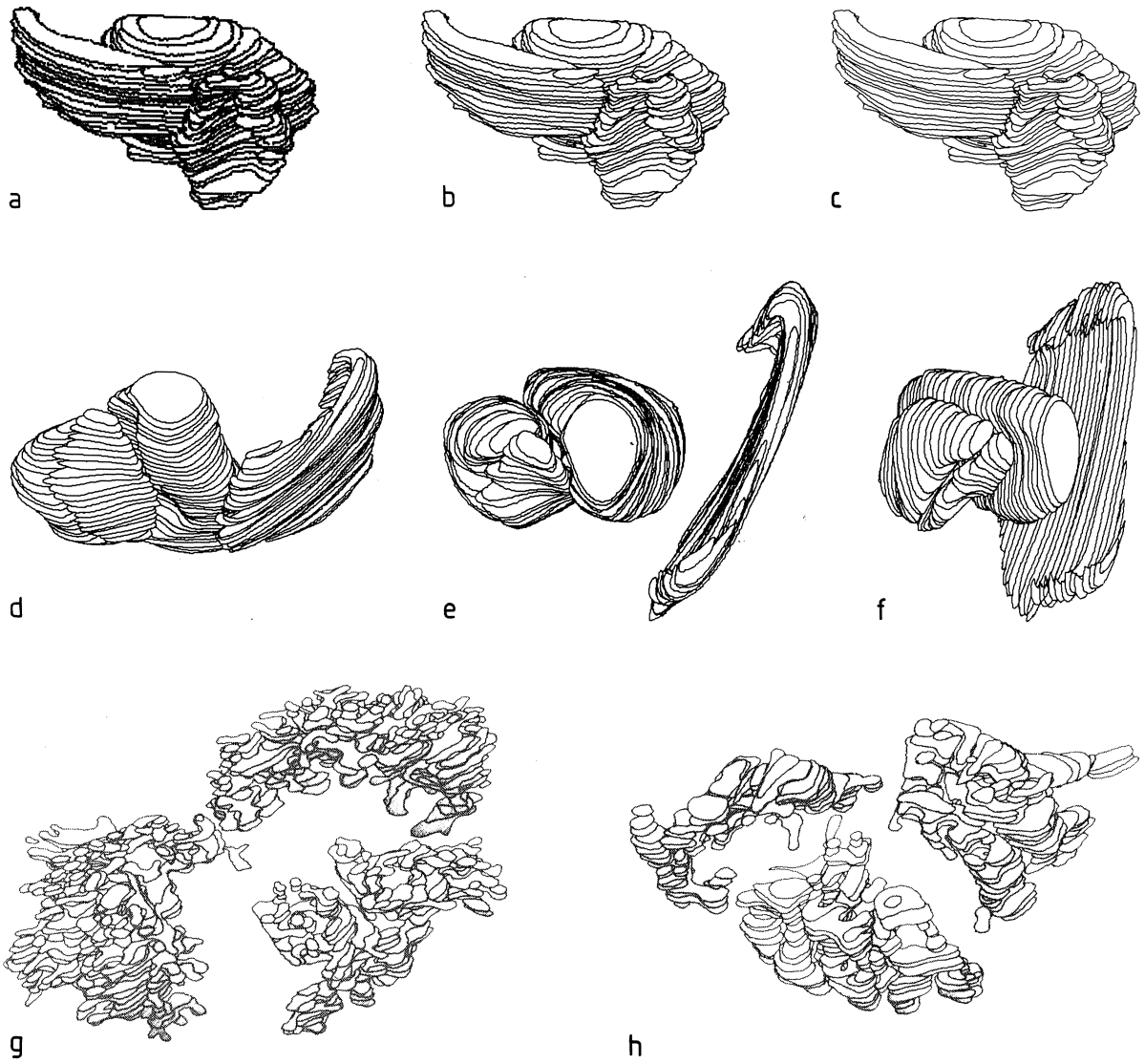


PLATE 8

Reconstruction of three dimensional objects from serial sections with hidden-line removal.

Low, medium and high resolution representation of the same view (a) 256, (b) 512, and (c) 1024 picture elements per line (optic lobe neuropil of the fly).

Three different views of the same object (d) tilted forward by 60^{o}, (e) from top, and (f) tilted right by 60^{o} (for details see text).

Reconstructions from serial sections of cells in the fish retina obtained by electron microscopy (g-h, for details see text).

of three-dimensional structure from electron micrographs (a large ill-posed linear problem) and from fibre diffraction data with heavy atom derivatives (a large nonlinear problem), the latter in collaboration with D. Marvin's group.

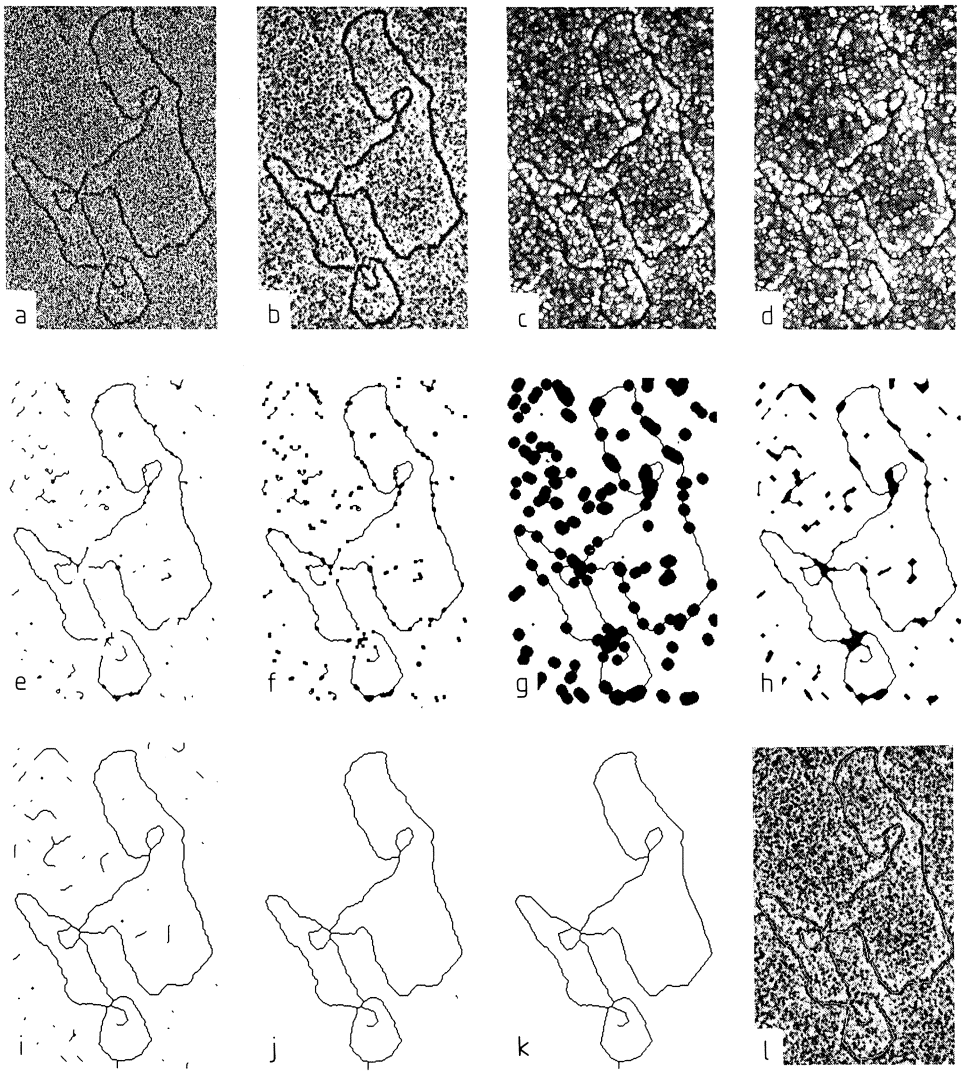
Another portable Fortran package implementing a new method for the reliable analysis of data represented by a sum of one-parameter functions, such as exponentials or convoluted exponentials in fluorescence decay, should be ready for distribution in 1981. A procedure was developed for a principal components analysis of two-dimensional data and applied to the analysis of solution x-ray kinetic data (from the M. Moody group) for evidence of intermediates.

Collaboration continued with H. Lehrach on the handling of nucleic acid sequence data. Hidden-line removal was implemented in the neurographics package to improve the two-dimensional display of three-dimensional reconstructions from serial sections and was applied by the N. Strausfeld group (Plate 8) and by H.-J. Wagner of Ulm. The method for automatically recognizing DNA molecules in electron micrographs was made more flexible by some new image pre-processing techniques; Plate 9 illustrates these with a protein-free mica preparation provided by H. Delius.

PLATE 9

Automated recognition of DNA strands in mica preparations.

The original image (a) of a sample DNA strand scanned at 25 μm film resolution is low-pass filtered (b) and repetitively thinned as a grey-tone image (c-d). After threshold slicing (e) the knot- and end-points are selected (f) for circular dilation (g). Repetitive thinning (h-i) is applied a second time followed by the proper recognition step, which renders the DNA strand as the largest connected image component (j). After final line smoothing (k) accurate measurements (e.g. of length) can be performed. Image (l) shows the resulting line graph superposed on the low-pass filtered image.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2.4.4. Computer group

Members: R. Herzog*, M. Albrecht, H. Bosshard, C. Boulin, F. Herzog*, D. Iversen, R. Kempf, T. Pitt, H. Struve

The computer group provides in-house computer facilities for general access and for certain special activities such as STEM picture analysis and molecular graphics. It takes care of the maintenance and extension of operating software and general utilities, file back-up, documentation, and development of, and program support for, special data acquisition peripherals.

During the past year programming efforts were mainly devoted towards the dedicated installations for STEM picture analysis and for interactive molecular graphics. Two well-developed program packages for special applications were implemented, namely SEMPER, an image-processing package developed in the Cavendish Laboratory, Cambridge, and the FRODO molecular modelling package of T. Alwyn Jones. Both packages needed some modifications and alterations to adapt them to our machines. Further extensions of these programs have been made as required by the specific research projects that make use of them.

After completion of the hardware interface to the STEM, both system and user software were developed and released in September 1980 (in collaboration with B.M. Unitt). This now permits the STEM to be operated at its highest speed, in both low-dose and electron-counting modes of operation.

To further enhance the performance of the STEM computer, an array processor had been connected to it during the previous year. Support software to improve the performance of the system, to speed up interactive analysis runs, and to simplify them, is needed. This work is now in

progress, and will continue throughout the coming year.

The graphics software has been adapted to the NORD machine as much as possible, but in view of the hardware limitations of the system it is not worth while putting still more effort into this. The arrival of the medium-sized 32-bit computer (VAX 11/780) will allow a different solution to the present problems during the latter part of the coming year.

Meanwhile, much work was devoted to developing an extended version of a FORTRAN pre-processor language, called RATMAC, which allows the use of "macros" and extended structured programming techniques in applications programming in a high level language. Well-written programs are to a large extent self-documenting - they describe in a straightforward way the method by which the problem is solved - and pre-processors help users to write their programs better.

The hardware group continued the development of the STEM interface, and has produced a number of test modules which have speeded up the actual installation. Work on data acquisition systems for x-ray detectors for the Hamburg outstation continued, with improvements being made for the linear detector, and a completely new two-dimensional detector read-out system being developed. Other projects include a hardware data reduction unit for crystallographic applications at Hamburg, and an attempt at the direct reading of radio-isotope marked bands in electrophoresis gels scanned with a linear position sensitive detector.

It has already been noted (p. 9) that Richard Herzog, Head of the Computer Group since its inception, left the staff in September 1980. Summing up the balance sheet of his four and half years' service to the Laboratory, he writes "during my stay at the EMBL, I formed and organized the Computer Group and its activities, as has been described in this and previous Reports. These Reports do not reflect all the

underlying activities which have to take place in order to maintain high-level professional work in relation to the computer field.

Documentation is usually the weak link in academic and research institutions: we produced 11 internal reports, 54 software notes, 23 user notes, 29 image-processing notes, and other user-oriented documentation of various kinds.

While responding to our local users' needs, we also distributed our system software and documentation widely throughout the community of NORD computer users: our back-up system is in daily use at more than 60 institutions in California, France, the U.K., Sweden, the Netherlands, Norway and CERN. Our text processor, and many other system utilities, are in constant use in more than 20 institutions. We have maintained regular exchanges with several divisions of CERN, with the Universities of Uppsala (BMC) and Göttingen, with the Central Institute for Industrial Research (Oslo) and with JET (U.K.), as well as heavily participating in the NORD user society NOCUS."

2.4.5. Instrumentation support for applications of synchrotron radiation

In 1979 certain areas of instrument development for applications of synchrotron radiation were brought together in Heidelberg in an effort to concentrate as much as possible the resources available for this important activity. As a result, considerable improvements in the performance of position-sensitive detectors were made. The processed count rates for the single wire linear detector were increased by a factor of ten, making the data acquisition rate for these detectors higher than 100,000 events per second. In this year the development was focussed on parallel wire arrays. With a fast parallel counter array and a two-level data store data rates of many millions of events per second have now been achieved. Further development of detector systems is now again being undertaken at the Outstations, with staff support from the Instrumentation Division. A. Gabriel and F. Dauvergne continue the improvement of two-dimensional systems in Grenoble, where it is easier to draw on similar technical developments in particle detectors at ILL and at CERN. J. Hendrix investigates multiple-event recording and counting systems at the Hamburg Outstation, where special schemes for efficient area detector readout for crystallographic applications are worked out with the local staff scientists.

A second major support project, carried out by the technical bureau in Heidelberg in collaboration with J. Bordas, M. Koch and H. Stuhrmann from the Hamburg Outstation, was the design of the special vacuum containers and the remotely controlled mechanics of the x-ray optical system for the new beamline on the electron side of the storage ring DORIS. This equipment will be installed in the Hamburg HASYLAB in the beginning of 1981.

2.4.6. Application of lasers

Member: R.W. Wijnaendts van Resandt

Technical assistants: D. Layer*, H.J. Marsman

The picosecond laser system, consisting of a synchronously-pumped dye-laser, was installed in April and fully operational by the end of May. A complete data acquisition and on-line analysis system for optical measurements, based on a Data General MP200 microcomputer system, was constructed and completed, including interfaces and software. The source delivers picosecond pulses (pulse width < 10 ps) with variable repetition rates up to 82 MHz and power up to 2 kW in the optical range 250-700 nm. Three applications were begun during the year:
(1) fast intensity correlation measurements in the range between ~10 nsec and 10 psec,
(2) dynamic fluorescence depolarization, and
(3) construction of a laser microprobe.
Some preliminary experiments were carried out on intensity correlation. The results show that it is essential to collect as much of the scattered light as possible. Further experiments await the completion of the light collection system. The dynamic fluorescence depolarization experiment has been set up and is operational. In the system used the horizontal and vertical polarized light are measured simultaneously by the same detection equipment. The technique has been tested by measuring the rotational diffusion of rhodamine 6G (excitation at 600 nm) and coumarine-1 and N-acetyl tryptophanamide (excitation at 300 nm). The measured diffusion times range from 30 to 600 psec. As a side product the fluorescence lifetime is measured in the nanosecond range (Wijnaendts van Resandt & De Maeyer, 1981).

The laser microprobe has been designed in collaboration with G.J. Brakenhof (Department for Electron Microscopy and Molecular Cytology, University of Amsterdam) and is now under construction. The microscope will have a field of view of 5 mm and, with 300 nm excitation, a resolution of about 100 nm.

Reference

Wijnaendts van Resandt, R.W. & de Maeyer, L.C.D. (1981). Chem. Phys. Lett., (in press).

2.4.7. Development of microanalytical techniques

Member: W. Ansorge

Visiting workers: P. Cantatore*, M. Drummond*, T. Knott*, S. Rasmussen*

Technical assistants: R. Barker*, J. Dickson*, Kim Lock-Song*

Work on improvements in DNA and protein electrophoresis on very thin (0.05-0.2 mm) thermally-stabilized polyacrylamide gels (Ansorge & De Maeyer, 1980) has continued. The device for casting very thin gels by a sliding technique has been further developed for the preparation of gels of 1 m or more in length for tests in DNA sequencing. Gels as little as 0.01 mm thick can be prepared with the sliding technique and these are well adapted for analytical isoelectric focussing. The design of the thermostatically-controlled platen has been optimized and simplified by a choice of suitable materials taking into account safety requirements for operation at high electrical fields. The chemical process developed for binding the thin gels to their support has been shown to be reliable on glass for practically all gel concentrations and buffers. New processes have been tested to improve the adhesion of polyacrylamide gels to polyester foil, mainly in the low concentration range (3-5%) and for gels containing urea. For sample loading a pneumatic system has been developed which should be useful especially for radioactive samples.

The DNA-sequencing technique on very thin thermostatically-controlled gels (in collaboration with H. Garoff) has been developed into a routine procedure (Garoff & Ansorge, submitted for publication). Studies are in progress of the effects of specimen quality and of the physico-chemical parameters of the gel on resolution.

The procedure developed for protein separation on very thin gels is fast (35 min on a 20 cm long plate), gives sharp bands and is very sensitive. The sensitivity has been further increased by a factor of 20, by adaptation and modification of the silver-staining technique (Ansorge, 1980), amounts as low as 5×10^{-10} g of protein per band being resolved. Two-dimensional separation procedures have been simplified, especially the isoelectric focussing step, by using the sliding gel casting technique. Tests have begun on the immunological detection and identification of antigens on very thin gels.

Micro-injection into cells is a new project of the group, with the aim of developing the manual technique of Graessmann et al. (1980) into a semi-automatic system with control of the displacement and the amount injected. The initial work has been concerned with the reliable and reproducible preparation of capillaries (tip diameter 0.0002-0.001 mm) and with their micromanipulation in a stable and vibration-free manner. A pneumatic system for injection has been designed and tested with living cells.

References

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Graessmann, A., Graessmann, M. & Müller, C. (1980). Methods in Enzym., 65, 816-825.

2.4.8. Magnetic separation

Member: T. Reed

Technical Assistant: A. Cockroft

A detailed study of the kinetics of a biological cell binding to low concentrations (3.3% to 14%) of sensitized adsorption beads was completed. The system was shown to follow pseudo-first-order kinetics with cell concentration as the free variable. The rate of reaction is quite rapid and will support flow-type separation devices using small volumes of adsorption beads (3% -14% of the reactor volume). This hitherto unobserved kinetic behaviour was shown also to apply in cases where the reactive cells were "diluted" by nonreactive cells.

Two types of "open array" of adsorption beads have been investigated. In the static array system, the magnetic beads are bound to wires by magnetic gradients produced by inserting the section of the flow tube containing the wires between the poles of a conventional electromagnet. It has been shown that a very low field strength (100-300 Gauss) is sufficient to bind the beads to the wires. A static array device is now being constructed for binding studies and separations using flowing suspensions of cells.

The dynamic array has been studied by computer simulation of the magnetic fields within solenoids with various types of pole piece and iron jacket arrangement, to optimize the "magnetic bottle" effect. Programs have been designed which not only permit the magnetic field distribution within the solenoid-surrounded flow tube to be determined, but which also show the forces acting on the individual magnetic particles at any place within the magnetic field of the solenoid. In this way it has been possible to design flow tubes that avoid magnetic anomalies which would immobilize the magnetic beads on the walls of the flow tube and defeat the purpose of a magnetic bottle. A

dynamic array system based on the magnetic bottle principle is being constructed and will be used for flow and separation studies.

Five magnetic separation devices for use in radio-immuno-assay and similar techniques have been constructed. After evaluation they were modified to use stronger magnets. These will be distributed to members of the laboratory for further evaluation.

2.5. The Outstation at the DESY, Hamburg

Head: H.B. Stuhrmann

(the other personnel and visitors to the Outstation are listed separately on p. 136 below)

After the first boom in successful synchrotron radiation experiments in 1979 the new horizons were explored more carefully. 1980 was as favourable as 1979 with respect to the availability of synchrotron radiation beam time. DORIS was operated for a total time of 40 days under optimal conditions for the EMBL (80 mA positron current at 3.3 GeV). For nearly 100 days the storage ring also emitted useful radiation during high-energy physics experiments (10-20 mA particle current stored at various energies between 3.7 and 4.6 GeV).

The research program of the Outstation continued to cover the following areas:

protein crystallography - low temperature studies, anomalous dispersion (X11);

small-angle scattering - time-resolved studies (X13), anomalous dispersion (X15);

high resolution x-ray spectroscopy (S11);

nuclear scattering (P11).

For descriptions of the instruments X11, X13, X15, S11 and P11 see the Annual Report for 1978. A description of some typical experiments carried out with most of them is given below.

Since the storage ring is now operated as a part-time dedicated synchrotron radiation source, more and more preference is given to the storage of electrons (see Annual Report, 1979). It appears that in 1981 DORIS will be operated as a synchrotron radiation source almost exclusively for a period of five months. Once the EMBL has installed the three planned new instruments in the Hamburger Synchrotrons-

strahlungslabor (HASYLAB), the radiation can be fully used. At present DESY still provides a positron current in DORIS to keep the EMBL experiments going. However, this will be reduced in the future.

Some selected research projects

Only few characteristic research projects are presented here. The complete list of projects is given in Table 2.

Protein crystallography (X11)

As exposure times in diffraction data collection from protein crystals with synchrotron radiation are very short, even with photographic film (typically around 1 min per degree of rotation, the total time needed for a complete data set often being determined by the exchange rate of film cassettes), systematic study of protein structures as a function of important thermodynamic variables (temperature, pressure, etc.) is greatly facilitated. It is for this reason that low temperature x-ray diffraction studies have been started in the laboratory.

Study of the flexibility of trypsinogen at -100°C

R. Huber, W. Bode, J. Walter (MPI für Biochemie, Martinsried), H.D. Bartunik.

A full data set at 1.6 Å resolution was collected from a trypsinogen crystal cooled to -100°C (wavelength 1.07 Å; the total time needed for data collection was about 3 hours). Evaluation of the film data gave a merging R-factor of 6%. Combined difference-Fourier and energy refinement yielded a R-factor of 19%. As compared to the room temperature structure more water molecules could be localized. Group temperature factors were derived and discussed in terms of intramolecular dynamics (manuscript in preparation). The study will be continued at an even lower temperature near -200°C.

Time-resolved x-ray diffraction studies of contracting frog muscle

H.E. Huxley, A.R. Faruqi, M. Kress (MRC, Cambridge); R.M. Simmons (Univ. College, London); J. Bordas, M.H.J. Koch.

The high intensity of the x-ray flux from the storage ring DORIS has enabled very rapid time-resolved measurements to be made on contracting muscle and some of these have been described in previous reports. Improvements in the data collecting system have now extended these measurements so that changes in many of the principal low-angle x-ray reflections from muscle can be followed with a time resolution of one millisecond or less (Plate 10). Large changes in the intensity of the 143 Å meridional reflection (from the myosin cross bridges) occur on this time scale during rapid releases or stretches of the muscle in which adjacent actin and myosin filaments undergo relative longitudinal displacements of 100 Å or less. These changes are now being analysed in detail, but they already provide evidence of a more direct kind than has hitherto been available that the active sliding of actin filaments past myosin filaments during contraction is produced by longitudinal movement of attached cross bridges.

Microtubule assembly studied by time-resolved x-ray scattering

E. Mandelkow, A. Harmsen, E.M. Mandelkow (MPI für medizinische Forschung, Heidelberg), and J. Bordas.

The high flux x-rays emitted by the storage ring DORIS have been used extensively for macromolecular relaxation studies. Among these the assembly of microtubules will be reported here. The structural transition of the protein aggregates during assembly from their subunits in solution is brought about by changes of temperature. The x-ray pattern at $4^{\circ}C$ arises from a mixture of tubulin rings, dimers and some other species. Raising the temperature to $36^{\circ}C$ induces the breakdown of rings followed by the growth of microtubules. It appears that microtubules are formed from tubulin oligomers smaller than rings (Plate 11). Though the depolymerization is not the exact inverse of

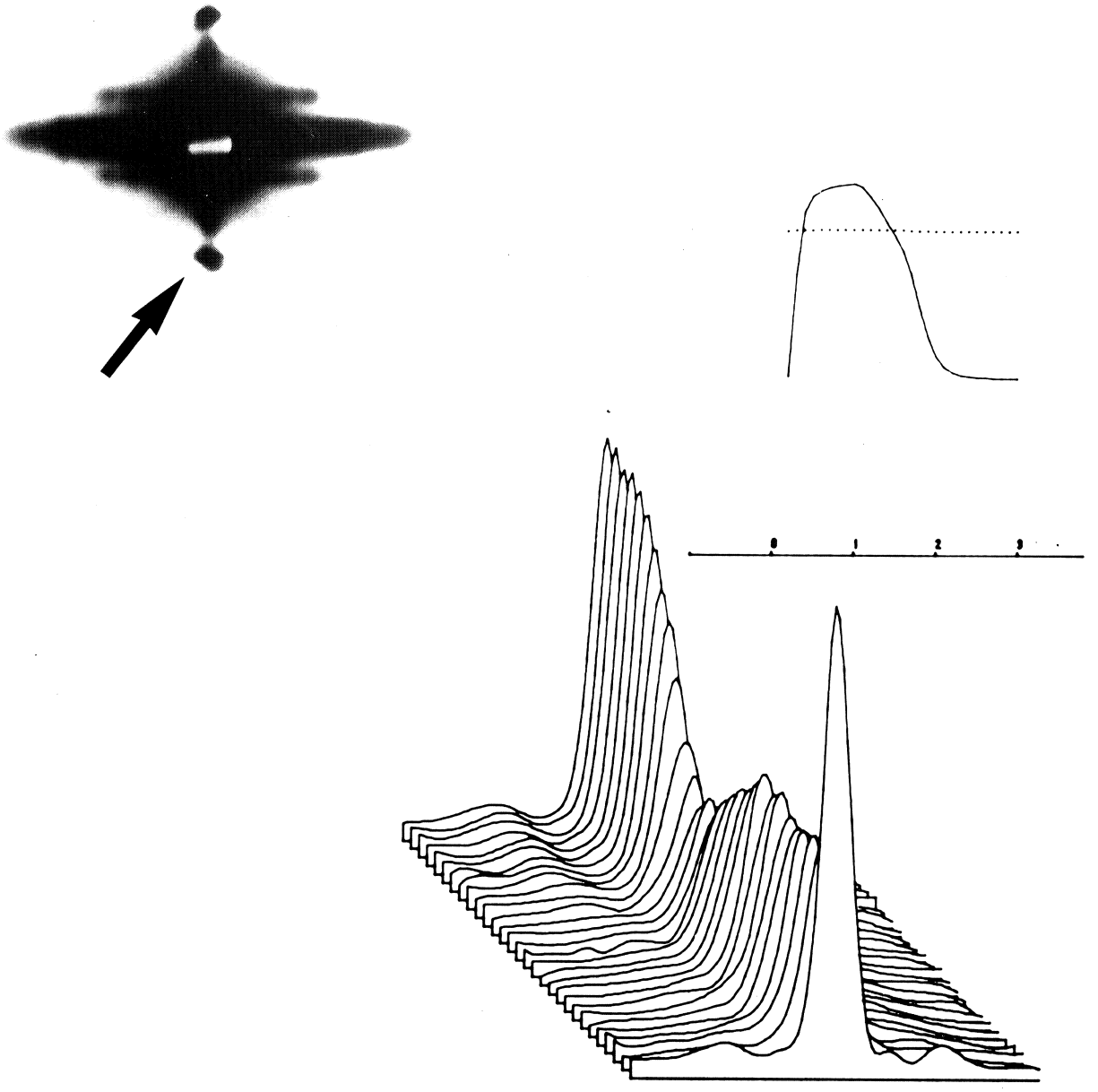


PLATE 10

Diffraction pattern of a frog sartorius muscle (top). The arrow points to the meridional reflexion at 143 Å. The diagram (bottom) illustrates the intensity change of this reflexion recorded with a linear Gabriel detector during an isometric contraction (time resolution 5 ms). The insert shows the tension in (full line) and the length of (dotted line) the muscle which are recorded simultaneously with the x-ray diffraction pattern.

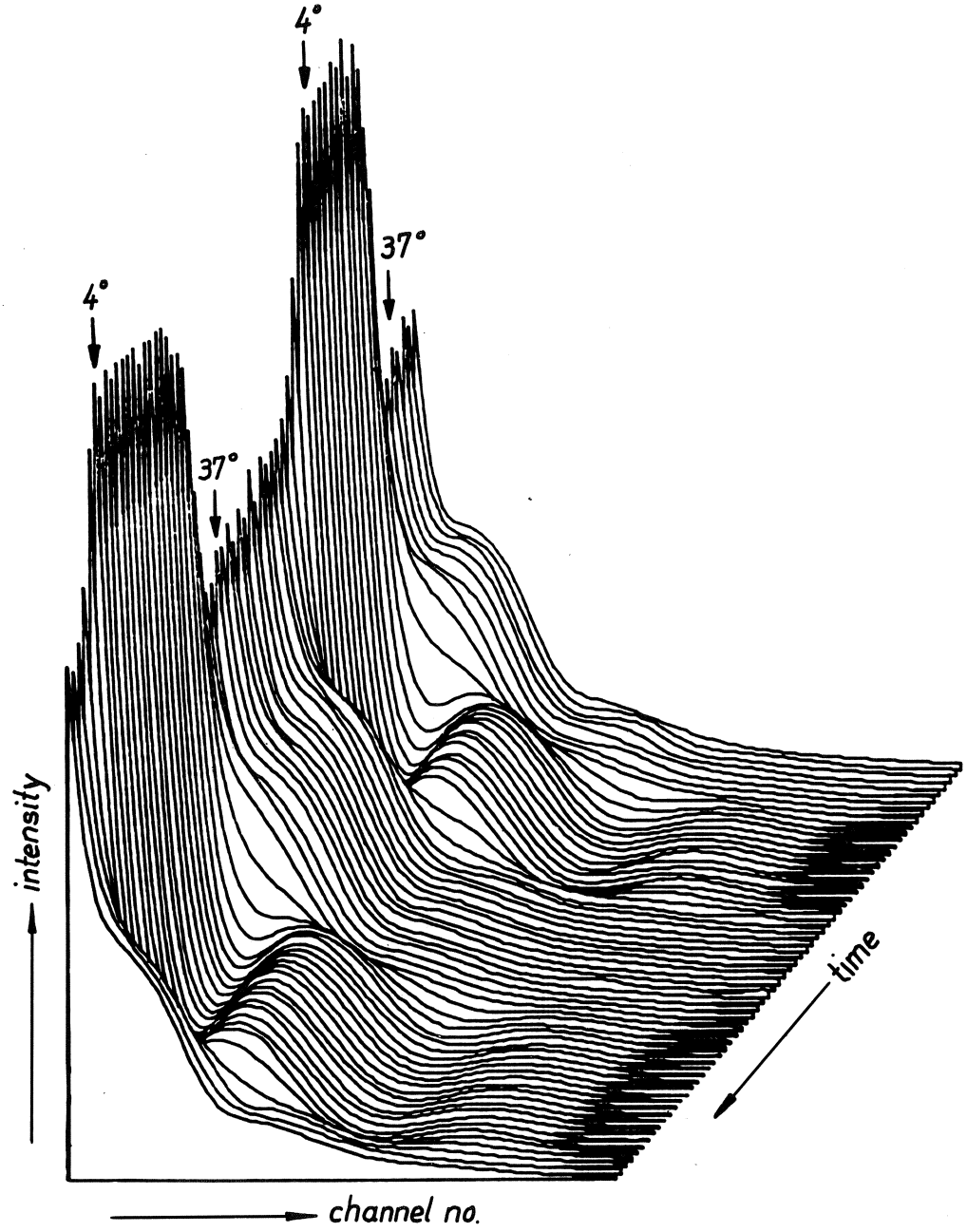


PLATE 11

Composite view of scattering traces obtained during two cycles of polymerization. Intensities were accumulated over time frames of 15 s, but only alternate frames are shown here. Temperature changes are as indicated. The half time of the T-jump is 25 s. Specimen-detector distance 320 cm, detector bin size 0.31 mm (80 mm per 256 channels). Note the changes in the height of the central scatter (left) and in the positions of the subsidiary maxima. The central scatter terminates abruptly owing to a lead beam stop in front of the detector.

polymerization, the cycles of assembly and disassembly can be repeated until the GTP is depleted. This applies to solutions of microtubule protein prepared in the absence of glycerol, with concentrations around 10-20 mg/ml. It is also important to note that the structures formed and their kinetics of polymerization do not seem to suffer significantly from radiation damage during the experiment.

The configuration of the four iron atoms in dissolved human haemoglobin as studied by anomalous dispersion

H.B. Stuhrmann, H. Notbohm (Univ. of Lübeck).

The anomalous dispersion of iron at its K-absorption edge in small-angle scattering of an aqueous solution of haemoglobin has been used to establish the geometrical arrangement of the four iron atoms in this protein. Though the anomalous contributions are about 0.001 to 0.01 of the total scattering, experiments with synchrotron radiation from the storage ring DORIS have shown that these effects can be measured with an average precision of about 10% at each of the 50 points of the scattering curve (Plate 12). The anomalous scattering represents the convolution of the whole structure with the configuration of the four iron atoms of haemoglobin (Plate 13). The analysis in terms of multipoles suggests that tetrahedral symmetry of both the subunit arrangement and the iron structure is a dominant feature. The mean distance of 26 Å between the iron atoms as derived from this experiment compares well with those derived from crystallographic data. A concentration of 20 mM iron was necessary to detect anomalous scattering of iron at the K-absorption edge. Lower concentrations of anomalous scatterers could be used at L_{III}-edges where much higher values of f' and f''_{III} between 10 to 30 electrons at K-absorption edges are encountered. It is likely that the anomalous dispersion of phosphorus and sulphur will be of considerable interest, as these atoms are natural markers in nucleic acids and proteins respectively. It should also be noted that the anomalous dispersion curves of light

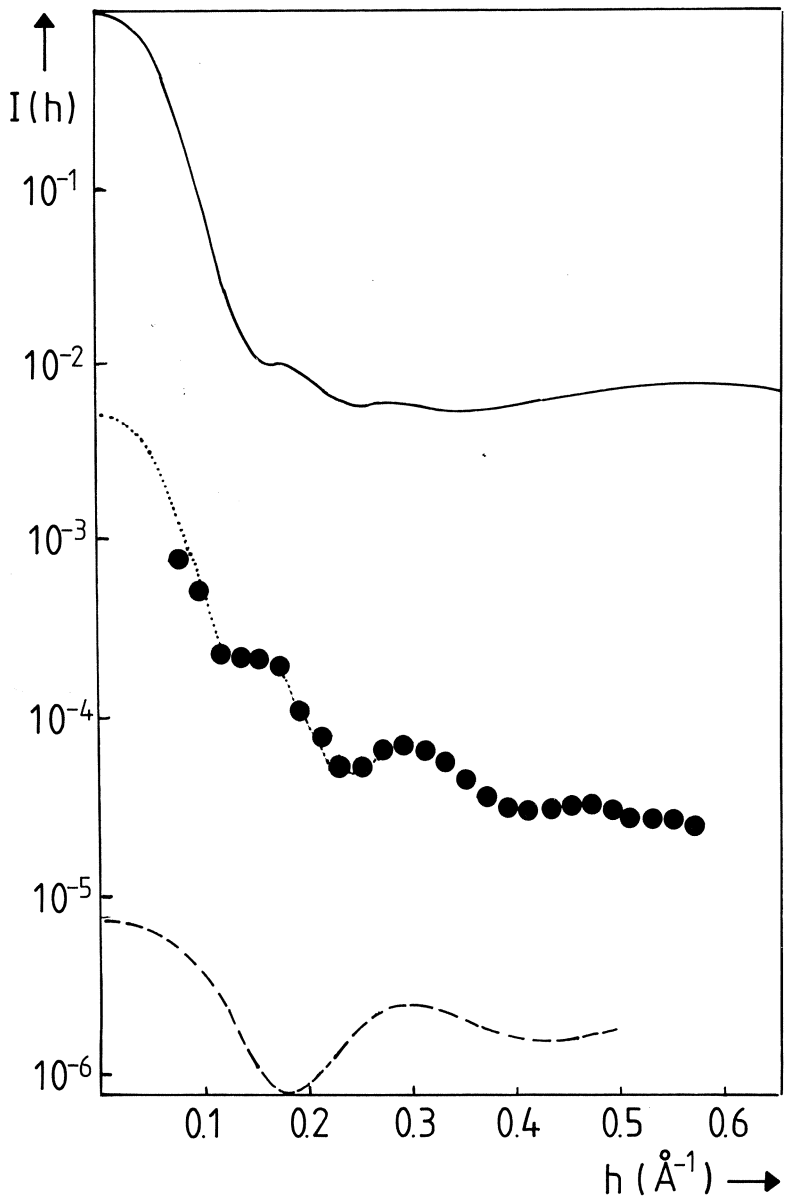
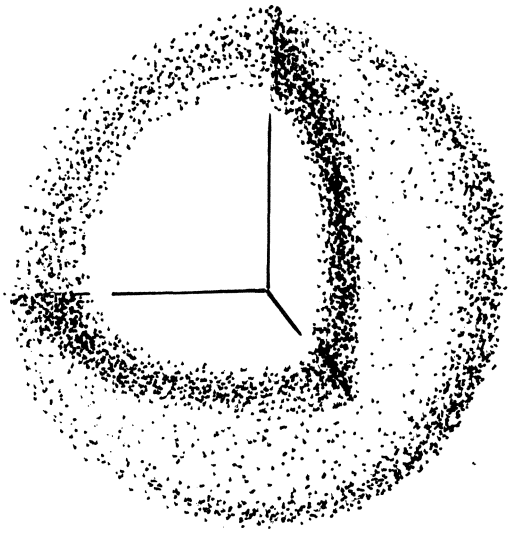
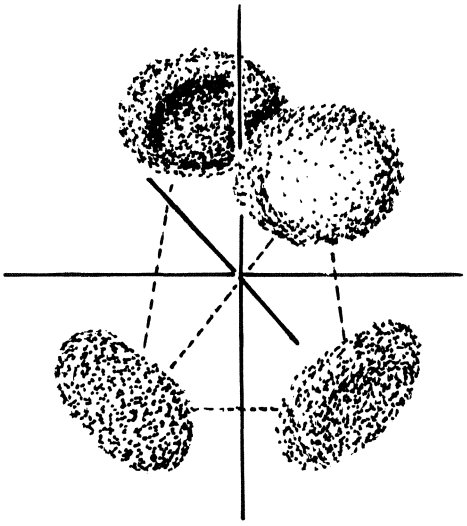


PLATE 12

The three characteristic scattering functions of the whole haemoglobin molecule, of the iron configuration alone, and the measured anomalous scattering of haemoglobin as a cross term. The cross term is deconvoluted in order to obtain the iron atom structure, as proposed in Plate 13.



monopole
l = 0



octupole
l = 4
m = 0, 3, 4

PLATE 13

The iron atom structure in dissolved human oxyhaemoglobin. The deconvolution of the cross term in Plate 12 is achieved in terms of a multipole expansion of the scatter, which immediately shows the dominant tetrahedral symmetry.

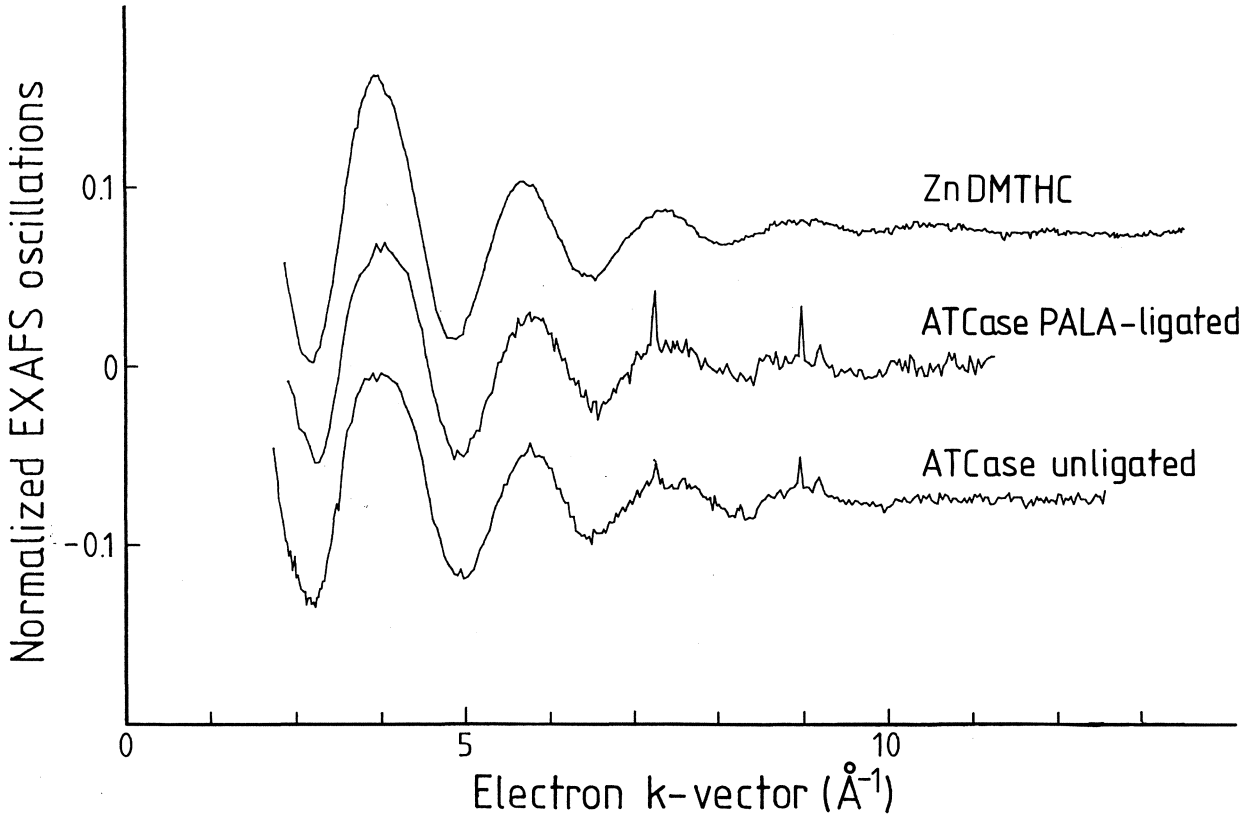


PLATE 14

Background-subtracted EXAFS spectra of the two forms of ATCase and a model compound. All three spectra are dominated by a single wave. The unligated and ligated spectra are identical. The model spectrum has the same frequency oscillations with the same phase but is slightly greater in amplitude. The zinc site in the two protein forms is therefore similar to the model except for either the number of ligands or the thermal damping factors. The latter explanation is more likely.

elements strongly depend on the chemical environment, which might make it possible to distinguish between atoms of the same element. Furthermore, anomalous scattering from polyelectrolytes was studied in order to elucidate the structure of the ionic environment. For instance, a 10% depression of the cross-section radius of gyration was observed in a 0.5% Cs-DNA solution at the L absorption edge of Cs (λ=2.47 Å). Rather encouraging results were also obtained from the anomalous scattering of erbium in membranes.

EXAFS (S11)

EXAFS studies of the zinc site in aspartate transcarbamylase

M.F. Moody, A. Foote (EMBL, Heidelberg), J. Phillips, J. Bordas & M.H.J. Koch (EMBL, Hamburg).

The enzyme aspartate transcarbamylase (ATCase) is active as a hexamer and shows allosteric properties. Each subunit contains one zinc atom and the purpose of the EXAFS study, conducted by M.F. Moody's group (EMBL, Heidelberg), is to detect possible structural differences at the metal site between the unligated and activated enzymatic states. Spectra obtained in 1979 by absorption detection indicated possible differences. This conclusion was only tentative, however, as the signal-to-noise ratios in the spectra were low. The experiment was repeated in 1980 after the new fluorescence detection system was installed in order to obtain more reliable data. Spectra of the two forms of the enzyme were obtained by fluorescence detection in two days of main-user beam time. There was a great increase in quality from absorption data enabling it to be said with certainty that no change takes place. Shown in Plate 14 are spectra for the relaxed form and for the activated form, both by fluorescence detection. Also shown in the spectrum of a model compound, zinc dimethyldithiocarbamate. The improvement in quality from absorption to fluorescence was noticeable. The effect of monochromator "glitches" was also reduced in comparison with the previous absorption data. There is no noticeable difference between the spectra from

the two forms of the enzyme. The similarities between the enzyme spectra and the model spectrum indicate that the zinc site is also similar. Thus a zinc coordination sphere of tetrahedrally-arranged sulphur atoms is inferred.

P11 Tunable x-ray beam (λ = 0.83-0.88 Å, for Mössbauer scattering of ^{57}Fe-nuclei

C. Hermes, F. Parak, R.L. Mössbauer (Technische Universität, München), H.B. Stuhrmann with technical assistance by H. Ludwig (EMBL, Hamburg).

The aim of this experiment is to measure resonant nuclear scattering of Fe excited by synchrotron radiation. At the first stage of the experiment a non-dispersive double monochromator system was constructed and tested. The 111 plane of perfect single crystals of germanium and silicon was used for the selection of the 10 eV and 5 eV energy bands at 14.4 keV. Two ionization chambers, in front of and behind the second monochromator crystal, were used for intensity measurements. The experimental values agree with the theoretical ones within a factor two (Table 1). The energy of the monochromatic beam was scaled with respect to the absorption edges of krypton (K edge, 1.432 eV), mercury (L_{II} edge, 1.4215 eV) and gold (L_I edge, 1.4353 eV).

Table 1

	E_D (GeV)	T_D (mA)	I_1 (x/s/10eV)	I_2 (x/s/10eV)	I_{theor} (x/s/10eV)
Ge (111)	4.5	13.5	8×10^{10}	4×10^{10}	1.8×10^{11}
Si (111)	4.4	55	1×10^{11}	5.9×10^{10}	2.75×10^{11}

E_D, T_D, energy and current of positrons stored by DORIS. I_1, I_2, x-ray quanta per second and per 10 eV energy band, measured after the first and second monochromator, respectively. $I_{theor.}$, theoretically expected flux of x-rays.

Table 2

List of projects

Projects on X11

(a) Time-resolved muscle diffraction

Mechanism of contraction of insect flight muscle	R.S. Goody, K.C. Holmes (MPI, Heidelberg)
X-ray diffraction study of contracting crustacean muscle	Y. Maeda (EMBL, Heidelberg)

(b) Protein crystallography

X-ray crystallographic study of the catalytic subunit of aspartate transcarbamylase	M. Moody (EMBL, Heidelberg)
The use of anomalous dispersion methods in the crystallography of proteins containing zinc, iron, mercury and platinum - avian pancreatic polypeptide - rabbit plasma transferrin - α-crystallin	T.L. Blundell, P.L. Lindley, G. Taylor, I.J. Tickle, W.G. Turnell, G. Geodley, J. Husain (London)
X-ray crystallographic investigation of - phosphorylase 6 - ß-lactamase I - prothrombin fragment 1 - troponin C - prealbumin	D.C. Phillips, C.C.F. Blake, L.N. Johnson, A. Miller, M.Y. Adams, S.J. Oatley, K.S. Wilson, J. Burridge (Oxford)
Use of anomalous scattering to locate Zn in enzyme G	O. Dideberg, J.M. Frere, J.M. Ghuysen (Liège)
Data collection from native and derivative kallikrein crystals	W. Bode, Z. Chen, K.S. Bartels (Munich/Hamburg)
Low-temperature studies of elastase	W. Bode, H.D. Bartunik, E. Meyer, J. Walter (Munich/Hamburg)

High resolution structure determination of phospho-glycerate mutase	H.C. Watson, J. Warwicker (Bristol)
Structure and function of the glucose-6-phosphate isomerase	H. Muirhead, A. Achari, S.E. Marshall (Bristol)
High resolution structure of bacterial 6-phosphogluconate dehydrogenase	J. Helliwell (Keele)
Three-dimensional structure of ribulose diphosphate carboxylase	W. Sänger (Göttingen)
X-ray structure of the TU:GDP complex from E.coli	W. Kabsch, D. Suck (MPI and EMBL, Heidelberg)
High resolution structure of the skeletal muscle actin: DNAase I complex	W. Kabsch, D. Suck (MPI and EMBL, Heidelberg)
High resolution structure of catalase from Penicillium vitale	B.R. Melik-Adamjan, S. Borisov, B.K. Vainshtein, K.S. Bartels (Moscow/Hamburg)
Single crystal x-ray studies on ribosomal proteins with special reference to low temperature work and 1 Å radiation	R. Reinhardt, K.S. Wilson, S. White (Berlin)

Projects on X13

(a) Small-angle diffraction

X-ray diffraction from corneal collagen	G. Elliott, Z. Sayer, S. Whitburn, K. Meek (Oxford)
Intermolecular crosslinking of bovine collagen	K. Hornbech-Svendsen (Copenhagen)
X-ray diffraction by the lens of the eye and its individual proteins	J. Randall, J.M. Vaughan (Edinburgh, Malvern)

(b) Time-resolved measurements

Muscle

Time-resolved studies of contracting frog muscle	H.E. Huxley, M. Kress, A. Faruqi, R. Simons, (Cambridge/London)
Time-resolved x-ray diffraction from thin filaments in contracting frog muscle	M. Kress (MRC, Cambridge)
Cross-bridge configuration studied in hypertonic muscle as a function of time	J. Lowy, F. Poulsen (Oxford)
Assessment of the cross-bridges in insect flight muscle when ATP binds at sub-zero temperatures	R. Tregear, M. Clarke, C. Rodger (ARC, Babraham)

Collagen

Small-angle scattering from native and stained collagen fibres	T. Nemetschek, H. Riedl, (Heidelberg)

Solutions

Polymerization of actin	J. Bordas, M. Koch (EMBL, Hamburg)
Structural transitions in microtubule assembly	E. Mandelkow, E.M. Mandelkow (MPI, Heidelberg)
Slow kinetic x-ray solution scattering experiments with allosteric proteins	M.F. Moody, P. Vachette (EMBL, Heidelberg)
The DNA helix-coil phase transition with incorporated metal ions	J. Porta (Barcelona)
Time-resolved small-angle x-ray studies of the structural dynamics of charged and uncharged tRNA	R. Rigler, L. Nilsson (Stockholm)

Membranes

Kinetics of conformational phase transitions in lipid phases	J.L. Ranck, A. Moudden (CNRS, Gif-sur-Yvette)

EXAFS projects on S11

X-ray spectroscopic studies of the Zn-centres of sheet tubulin	J. Bordas, E.M. Mandelkow (EMBL, Hamburg/MPI, Heidelberg)
Determination by EXAFS of the Zn environment in enzyme G	O. Dideberg (Liège)
EXAFS studies of the copper centres in superoxide dismutase	D. Garner, N. Blackburn, S. Hasnain (Manchester/Daresbury)
X-ray absorption experiments on 2 Zn and 4 Zn insulin, carboxy-peptidase A, vitamin B12 and model compounds	J. Randall (Edinburgh)
EXAFS studies of metallo drugs and proteins	D. Sadler, A. Mazid (London)
X-ray absorption spectroscopy of copper proteins	T. Vanngard, K.E. Falk, B. Reinhammer (Göteborg)
EXAFS studies of the zinc atoms in aspartate transcarbamylase	M.F. Moody (EMBL, Heidelberg)
EXAFS studies of single crystals of myoglobin	M.F. Moody (EMBL, Heidelberg)
Copper-ligand distances in haemocyanin from H.pomatia	R. Torensma (Groningen)
EXAFS studies of yeast super-oxide dismutase	R. Bauer (Copenhagen)
EXAFS investigation of the iron centres in soy bean lipoxygenase	M. Feiters (Utrecht)

Projects on X15

Contrast variation studies of ferritin in CsCl solutions at the L absorption edge of Cs	H.B. Stuhrmann (EMBL, Hamburg)

Counter-ion distribution of Os-DNA from anomalous scattering	H.B. Stuhrmann, R. Oberthuer (EMBL, Heidelberg/Grenoble)
Phasing of diffraction pattern of Er-doped DPPC membrane by anomalous scattering of erbium	H.B. Stuhrmann, J. Phillips, G. Bueldt (EMBL, Hamburg/Basel)
Contrast variation studies of tryptophan synthase subunits in various anomalous scattering solvents	H.B. Stuhrmann, P. Bartholmes (EMBL, Hamburg/Regensburg)
Ion distribution in and near the 50S subunit of E.coli ribosomes	H.B. Stuhrmann, K. Nierhaus (EMBL, Hamburg/Berlin)
Anomalous scattering of iron in haemoglobin	H.B. Stuhrmann, H. Notbohm (EMBL, Hamburg/Lubeck)
Ion distribution of polyacrylic solutions	H.B. Stuhrmann, R. Obertheur, M. Rangetti (EMBL, Hamburg/Grenoble/Mainz)
Small-angle diffraction of ribosome crystals	A. Yonath, H.B. Stuhrmann (Rehovot/EMBL, Hamburg)
Small-angle scattering of ATPase solutions	T. Nawroth, H.B. Stuhrmann (Mainz/EMBL, Hamburg)

2.6. The Outstation at the ILL, Grenoble

Head: B. Jacrot*, A. Miller*

(the other personnel and visitors to the Outstation are listed separately on p. 140 below)

The Outstation was established to assist in the development of the use of neutron beams in molecular biology. This aim is being achieved in several ways:

- by providing expertise in neutron methods,
- by making accessible to neutron users ancillary physical techniques,
- by providing all biochemical facilities that are needed,
- by preparing deuterated organisms, as a source of deuterated molecules.

These four aspects imply that the Outstation has an important service activity. The quality of this service is made possible by the development of several lines of research chosen to create a coherent scientific activity in the laboratory and to use the existing facilities, in particular the neutrons. In consequence of the appointment of a new Head of the Outstation, the main emphasis of this research is shifting from studies on fibrous proteins (collagen and myosin) to virus structure and assembly.

In the collagen field the projects that are still continuing are now being carried out in cooperation with outside laboratories, and are mainly concerned with the reconstitution of collagen (Types I and II) in cooperation with D. Herbage (Lyon).

In the study of the primary structure of myosin, a periodicity in the distribution of methionyl residues has been found, and a better characterization of the fragments corresponding to that periodicity is under way.

A virus program had already existed in previous years in cooperation with J. Mellema (Leiden). This has led to an investigation of influenza virus by neutron and light scattering, which has shown that, contrary to prevailing beliefs, this virus has a well-defined spherical shape (diameter 1,060 Å), with a molecular weight about 220.10^6, much smaller than the values so far published. New developments are a study of a plant virus (brome mosaic virus) used as a model system to understand its self-assembly. This work, which is an EMBL-ILL cooperation, involves neutron scattering, x-rays and inelastic light scattering as well as biochemical approaches. The first series of results has shown under what conditions the protein alone self-assembles to produce a shell isomorphous with that in the virus. The kinetics of that process have first been studied with neutrons; the results suggest a very fast process (taking a few seconds) forming a shell of the right size but incomplete, followed by a very slow process (several hours) to complete the particle. These studies will be complemented by kinetic studies using light elastic and inelastic scattering, and x-rays.

Semliki Forest virus has been investigated, mostly with neutrons (in cooperation with H. Soderlund, Helsinki) to obtain a low resolution structure. A first result is that the molecular weight is about 42.10^6 smaller than previous estimates.

A newly started program deals with the conformation of RNA from viruses in solutions, as well as the folding of this RNA inside the virion. This also involves several physical techniques associated with biochemical methods such as cross-linking.

As mentioned above this in-house activity is carried out in parallel with activities in which the expertise of the staff and the equipment of the Outstation are called upon by visitors. A particularly important aspect of this activity is the production of deuterated material. The deuteration laboratory is being reorganized to

produce not only deuterated organisms (E.coli and Physarum), but deuterated components extracted from these organisms: ribosomes, nucleosomes, tRNA, enzymes involved in protein biosynthesis, lipids, deuterated amino acids, actin and myosin, etc. These molecules will be available for neutron and NMR users.

Among the ancillary techniques available x-rays and inelastic light scattering (photon correlation) are of special importance. A camera for small-angle scattering from solution and a precession camera have been set up and are widely used by visitors to the ILL. The light-scattering instrument has been provided with various facilities for the use of microcells, for kinetic experiments with stopped flow, and for measurements of turbidity and angular distribution.

The neutron expertise of the staff has been needed for several cooperative programs. Among the newer such programs may be mentioned the study of the matrix protein of the cell wall (with J.P. Rosenbusch, Basel). Here the neutron work was complemented by photon correlation, and leads to an understanding of the interaction between the protein and the detergent used to solubilize it. Again a study of cytochrome reductase (with H. Weiss, EMBL Heidelberg) is an interesting approach to a membrane protein, in which specific cleavages of parts of it are used to localize its various subunits. An experiment on melittin, solubilized or in the membrane, (with R. Strom, Rome) is another example of a study of a protein-lipid system.

Cooperation with the ILL is developing, especially with the biological groups. The EMBL and ILL staff complement one another, the latter being much more involved in instrumental and methodological development with neutrons. An example is low-resolution crystallography by contrast variation. This method, especially suitable for the study of viruses, nucleosomes and ribosomes, has been developed at the ILL, but in the future the EMBL will play a growing role in its application.

The new joint EMBL-ILL building, situated on the ILL site, is expected to be completed in October 1981. It will still further facilitate cooperation and the use of physical techniques both by the local staff and the numerous molecular biologists visiting the ILL.

The various items of ancillary equipment in the Outstation have been widely used by visitors, some of whom are listed below.

Photon correlation spectroscopy (M. Zulauf)

Homologous series of detergent micelles	J. Rosenbusch (Basel)
Solubilization of the matrix protein with detergent	J. Rosenbusch (Basel)
Diffusion coefficient of several strains of influenza virus	J. Mellema (Leiden)
The existence of two states of aggregation of melittin depending on pH and ionic strength	R. Strom, F. Podo (Rome)
The proteins of adenovirus II	C. Devaux (Lille)
Nitrogenase CP1	J. Meyer (CENG, Grenoble)
Tryptophansynthetase and its subunits	K. Kirschner (Basel)
Semliki Forest virus diffusion coefficient	H. Soderlund (Helsinki)

X-ray diffraction (C. Berthet)

Structure of collagen in cartilage	D. Herbage and collaborators (Lyon)
Interaction between melittin and artificial membranes	R. Strom, F. Podo (Rome)
Proteins of adenovirus (hexon, penton, fibre)	C. Devaux and collaborators (Lille)
Tryptophan synthetase and its subunits	K. Kirschner (Basel)

Alfalfa mosaic virus (solution study)	J. Mellema and collaborators (Leiden)
Tomato bushy stunt virus (solution study)	J. Witz and collaborators (Strasbourg)
Structure of the aspartyl tRNA-tRNA synthetase complex	D. Maras and collaborators (Strasbourg)

Biochemical facilities (F. Borras-Cuesta)

Visitors have for the most part used the amino-acid analyser (for determination of concentrations) and the analytical centrifuge. A determination, or a redetermination, of the absorbance, needed for neutron experiments, has been carried out using the amino-acid analyser for the following projects:

Adenovirus structural proteins (hexon, penton, fibre)	C. Devaux (Lille)
Semliki Forest virus	H. Soderlund (Helsinki)
Brome mosaic virus	M. Cuillel (EMBL, Grenoble)

Deuteration facilities (K. Simpson)

Ribosomal subunits	K. Nierhaus and collaborators (Berlin)

In addition various facilities have been used by visitors from the EMBL in Heidelberg, in the context of the neutron studies of the elongation factor Tu (R. Leberman and collaborators) and of cytochrome c reductase (H. Weiss and collaborators). In the latter project the Outstation also provided neutron expertise (S. Perkins).

3. Administration

To facilitate comparison, a summary of the financial situation is presented in two tables in the same form as last year. Table 3 summarizes the budgeted and actual expenses during 1980; staff costs and operating costs have further increased in comparison with 1979 whereas capital expenditure has further decreased. Table 4 which includes the Budget for 1981, gives an indication of general trends.

TABLE 3

SUMMARY OF THE LABORATORY'S BUDGETED AND ACTUAL INCOME AND EXPENDITURE DURING 1980

INCOME	BUDGET KDM	ACTUAL KDM	EXPENDITURE	BUDGET KDM	ACTUAL KDM
Carried forward from 1979	7,527	7,527	Staff Costs (including Internal Tax)	19,339	17,144
Liquidation of Reserve	2,942	2,942	Operating Costs	13,171	10,407
National Contributions	26,500	26,500	Capital Expenditure	5,646	5,633
Special Contribution of the Federal Republic of Germany	-	-			
Bank Interest	400	1,483	Reserve	2,801	2,801
Pension Scheme	624	577			
Internal Tax	2,944	2,953			
Unpaid Commitments and Other Income	20	625			
Total Income	40,957	42,607	Total Expenditure	40,957	35,985
Surplus		1,650	Provisions not spent or committed		4,972
TOTALS		40,957	TOTALS		40,957

TABLE 4

TRENDS IN THE LABORATORY'S INCOME AND EXPENDITURE 1979-1981

INCOME	BUDGET 1981 KDM	OUTTURN 1980 KDM	OUTTURN 1979 KDM	EXPENDITURE	BUDGET 1981 KDM	OUTTURN 1980 KDM	OUTTURN 1979 KDM
Carried forward from 1979	6,622	7,527	7,170	Staff Costs (net)	16,673	13,693	10,934
Liquidation of Reserve	2,801	2,942	3,437	Operating Costs	13,981	10,407	8,497
Ordinary Contributions	27,500	26,500	22,861	Capital Expenditure	6,245	5,633	7,444
Special Contribution Federal Republic of Germany	-	-	1,349				
Bank Interest	568	1,483	845	Reserve	672	2,801	2,942
Pension Scheme (previous years only)	-	79	279	Carried forward to following year	-	6,622	7,527
Other Income	80	625	1,403				
TOTALS	37,571	39,156	37,344	TOTALS	37,571	39,156	37,344

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PUBLICATIONS BY MEMBERS OF THE LABORATORY

Ansorge, W. (1980). Verfahren und Vorrichtung für Herstellung von sehr dünnen (0.02-1.5 mm) Gelen und ihre Anwendung in Elektrophorese; Silberanfärbung von Proteinen. In Elektrophorese Forum '80: Kurzfassungen der Vorträge: Heraus. Radola, B. J.; Technische Universität, München. p.67-74.

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Bartunik, H. D., Clout, P. N. & Robrahn, B. (1981). Rotation data collection for protein crystallography with time-variable intensity from synchrotron radiation sources. J. Appl. Cryst., (in press).

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PUBLICATIONS FROM LAST YEAR'S REPORT

Bordas, J., Koch, M.H.J., Clout, P.N., Dorrington, E., Boulin, C. & Gabriel, A. (1980). A synchrotron radiation camera and data acquisition system for time resolved x-ray scattering studies. J. Phys., E., 938-944.

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Schaller, H.C., Schmidt, T., Grimmelikhuijzen, C.J.P., Rau, T. & Bode, H. (1980). Morphogenetic substances in nervefree hydra. In Developmental and Cellular Biology of Coelenterates; eds. Tardent, P. & Tardent, R.; Elsevier/North Holland, Amsterdam, p.389-394.

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Tsugita, A., Van den Broek, R. & Gregor, I. (1980). Protein chemical approaches for the investigation of T4-head morphogenesis. BioSystems, 12, 225-238.

White, J. & Helenius, A. (1980). pH-dependent fusion between the Semliki Forest virus membrane and liposomes. Proc. Nat. Acad. Sci., USA, 77, 3273-3277.

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SEMINARS AND COURSES GIVEN BY MEMBERS OF EMBL

January

Deutsches Krebsforschungszentrum, Heidelberg, Federal Republic of Germany.
B.M. Jockusch, "Organisationsmuster von Mikrofilamenten".

University of Utrecht, The Netherlands.
B.M. Jockusch, "Organisation of contractile elements in muscle and non-muscle cells".

Colloque du CNRS sur les Membranes Biologiques, Les Arcs, France.
J. Dubochet, "Que nous apporte la microscopie électronique aujourd'hui".

DESY, Hamburg, Federal Republic of Germany.
H.B. Stuhrmann, "Synchrotronstrahlforschung der EMBL Aussenstelle Hamburg".

Laboratoire de Cristallographie, Institut de Physique, Université de Liège, Belgium.
M.H.J. Koch, "La diffraction cinétique appliquée aux systèmes biologiques".

Institut für organische Chemie und Biochemie, Universität Hamburg, Federal Republic of Germany.
H. Weiss, "Die energieüberführenden Oxidoreductasen der Mitochondrien".

Biochemisches Institut, Universität Zürich, Switzerland.
H. Weiss, "Die Struktur von elektronenübertragenden Multienzymkomplexen der Mitochondrienmembran".

Wallenberg Laboratory, Uppsala, Sweden.
H. Garoff, "Cloning and sequencing of the Semliki Forest virus genome".

University of Umeå, Sweden.
H. Garoff, "Cloning and sequencing of the Semliki Forest virus genome".

Research Institute, Pharmacology Department, Wakunaga, Hiroshima, Japan.
A. Tsugita, "Morphogenesis specific cleavage in T4 phage capsid".

Research Unit, Pharmaceutical Department, Shionogi, Osaka, Japan.
A. Tsugita, "A protease for morphogenesis specific cleavage in T4 phage".

National Institute for Genetics, Mishima, Japan.
A. Tsugita, "Phage capsid formation and recent development of protein chemistry".

University of Newcastle, England.
K. Murray, "Hepatitis B virus and the expression of its antigens in E. coli".

February

Laboratory of Physiological Chemistry, University of Leiden, The Netherlands.
B. Dobberstein, "Protein secretion in eukaryotic cells".

Department of Zoology, Universität Göttingen, Federal Republic of Germany.
J.-E. Edström, "Expression and suppression of differentiated functions in Chironomus salivary glands".

Centre de Génétique Moléculaire, Gif-sur-Yvette, France.
V. Pirrotta. "Cloning of Drosophila genes active during embryogenesis".

Institut für Biochemie, Chemisches Laboratorium der Universität München, Federal Republic of Germany.
H. Weiss, "Die Struktur von elektronenübertragenden Multienzymkomplexen der Mitochondrienmembran".

Philipps-Universität, Marburg, Federal Republic of Germany.
H. Reggio, "The role of sulphate polyamnions in the packaging of secretory proteins".

Max-Plank-Institut für Medizinische Forschung, Heidelberg, Federal Republic of Germany.
J. C. Phillips, "Synchrotron radiation anomalous dispersion studies of biological materials".

Molecular Biology IIIa, University of Edinburgh, Scotland.
K. Murray, Introductory lecture on "Molecular Biology".

March

Universität Heidelberg, Federal Republic of Germany.
C. Nüsslein-Volhard, "Genetische Analyse der Musterbildung in Drosophila".

Universität Freiburg, Federal Republic of Germany.
C. Nüsslein-Volhard, "Genetische Analyse der Musterbildung in Drosophila".

Max-Planck-Institut für Biochemie, Martinsried/München, Federal Republic of Germany.
B.M. Jockusch, "Organization of contractile elements in muscle and non-muscle cells".

Department of Bacteriology, Karolinska Institutet, Stockholm, Sweden.
H. Weiss, "The use of detergents for isolation and characterisation of membrane proteins".

Department of Biochemistry, University of Stockholm, Sweden.
H. Weiss, "The structure of mitochondrial electron transfer complexes".

University of Utrecht, The Netherlands.
H. Reggio, "Membrane endocytosis in the rat pancreas and in cultured epithelial cells".

Hubrecht Laboratory, University of Utrecht, The Netherlands.
D. Louvard, "Mécanismes moléculaires impliqués dans la biogénèse de la surface cellulaire de cellules épithéliales en culture".

April

Centre de Recherches sur le Cancer, Villejuif, France.
K. Murray, "Hepatitis B virus and the expression of its antigens in E. coli".

Universität Heidelberg, Federal Republic of Germany.
B. Dobberstein, "Synthese, Einbau in die Membran und intrazellulärer Transport von Histokompatibilitätsantigenen".

Institute for Molecular Biology II, University of Zürich, Switzerland.
J.-E. Edström, "Determination and induction of giant secretory proteins in Chironomus".

Institut de Biochimie, Orsay, France.
D. Louvard, "Mécanismes moléculaires impliqués dans la biogénèse de la surface cellulaire de cellules épithéliales en culture".

Institut für Organische Chemie, Universität Düsseldorf, Federal Republic of Germany.
H. Weiss, "Struktur von elektronenübertragenden Multienzymkomplexen der Mitochondrienmembran".

Max-Planck-Institut für Molekulare Biologie, Tübingen, Federal Republic of Germany.
A. Helenius, "Mechanisms of animal virus entry into cells".

May

Institut für Kommunikationstechnik, Eidgenössische Technische Hochschule, Zürich, Switzerland.
P.T. Speck, "Automatische Extraktion von Linienstrukturen aus Rasterbildern".

Laboratoire de Génétique Moléculaire des Eucaryotes du CNRS, Strasbourg, France.
P.T. Speck, "Extraction of line structures from noisy images".

Biozentrum, Basel, Switzerland.
C. Nüsslein-Volhard, "Segmentation in Drosophila: a genetic analysis".

Institut de Biologie Moléculaire, Strasbourg, France.
J. Dubochet, "La microscopie électronique au LEBM".

Department of Microbiology, Universität Heidelberg, Federal Republic of Germany.
M. Zabeau, "A genetic analysis of the EcoRI restriction and modifiation system".

Universität Heidelberg, Federal Republic of Germany.
M.H.J. Koch, "Die Synchrotronstrahlung und ihr Einsatz bei Strukturuntersuchungen an Biopolymeren".

Deutsches Krebsforschungszentrum, Heidelberg, Federal Republic of Germany.
H. Garoff, "Cloning and sequencing of the Semliki Forest virus genome".

Institut Pasteur, Paris, France.
H. Garoff, "Cloning and sequencing of the Semliki Forest virus genome".

Institut für Molekulare Genetik, Universität Köln, Federal Republic of Germany.
K. Simons, "The life cycle of a membrane virus".

Department of Cell Biology, Yale University, New Haven, Conn., USA.
A. Helenius, "Virus entry into tissue culture cells".

Wallenberg Laboratory, Uppsala, Sweden.
A. Helenius, "Membrane reconstitution".

University of Lund, Sweden.
A. Helenius, "Virus entry into cells".

University of Helsinki, Finland.
A. Helenius, "Mechanisms of virus entry into host cells".

Institut für Molekularbiologie der Österreichische Akademie der Wissenschaften, Salzburg, Austria.
H. Lehrach, "Cloning and sequence analysis of Semliki Forest virus 26S mRNA".

Max-Planck-Institut für Biophysikalische Chemie, Göttingen, Federal Republic of Germany.
H. Lehrach, "Cloning and sequencing techniques".

Department of Zoology, University of Pavia, Italy.
G. Geiger and D. Nässel, "Aspects of visually guided behaviour and histology of the visual neuropils in Musca mutants".

June

Swiss Institute for Experimental Cancer Research, Lausanne, Switzerland.
B. Dobberstein, "Structure and biosynthesis of histocompatibility antigens".

Physikalisches Institut der Universität Giessen, Federal Republic of Germany.
R.W. Wijnaendts van Resandt, "Position-sensitive detection in atomic physics".

Département de Biologie Cellulaire et Moléculaire, Université d'Aix/Marseille, Luminy, France.
V. Pirrotta, "Cloning of Drosophila genes active during embryogenesis".

Institut de Recherche en Biologie Moléculaire, Paris, France.
J. Dubochet, "Mounting biological particles for electron microscopy".

Lehrstuhl für Organische Chemie, Universität Dortmund, Federal Republic of Germany.
H. Weiss, "Die Struktur von elektronenübertragenden Multienzymkomplexen der Mitochondrienmembran".

Institut für Genetik, Universität München, Federal Republic of Germany.
H. Weiss, "Struktur von elektronenübertragenden Multienzymkomplexen der Mitochondrienmembran".

Corso di Ingegneria Genetica. Associazione Genetica Italiana, Cortona, Italy.
V. Pirrotta, Instructor.

Réunion de Travail sur la Mobilité Cellulaire, Banyuls, France.
D. Louvard, "Relations cytosquelette-membrane plasmique".

Institut Pasteur, Paris, France.
D. Louvard, "Mécanismes moléculaires impliqués dans la biogénèse de la surface cellulaire de cellules épithéliales en culture".

CERN Summer School, Malente, Federal Republic of Germany.
H.B. Stuhrmann, "Molecular biology and synchrotron radiation".

Rockefeller University, New York, NY, USA.
H. Garoff, "Structure and assembly of Semliki Forest virus".

MRC Laboratory of Molecular Biology, University Medical School, Cambridge, England.
K. Simons, "Cell exit and entry of Semliki Forest virus at the molecular level".

Institute of Immunology, Basel, Switzerland.
K. Simons, "How Semliki Forest virus enters and leaves its host cell".

Princeton University, New Jersey, USA.
H. Lehrach, "Cloning and sequencing of Semliki Forest virus 26S mRNA sequences".

Chester Beatty Research Institute, London, England.
K. Murray, "Some applications of genetic engineering".

July

Institut für angewandte Mathematik, Universität Heidelberg, Federal Republic of Germany.
R.H. Vogel, "Informationsverlust mit Transformationsmethoden bei der Systemidentifizierung".

University of Wisconsin, Madison, Wisconsin, USA.
H. Garoff, "Structure and assembly of Semliki Forest virus".

The Medical School, St. Louis University, St. Louis, Miss., USA.
H. Garoff, "Structure and assembly of Semliki Forest virus".

Salk Institute, San Diego, Calif., USA.
H. Garoff, "Structure and assembly of Semliki Forest virus".

Max-Planck-Institut für Biochemie, Martinsried/München, Federal Republic of Germany.
M. Zabeau, "The EcoRI restriction and modification enzymes: a model system for studying protein-DNA interactions".

Universität Heidelberg, Federal Republic of Germany.
H.D. Bartunik, "Study of the fast kinetics in three-dimensional structures with synchrotron radiation".

University of Barcelona, Spain.
J. Bordas, "Utilizacion de la radiacion sincrotronica en estudios estructurales (EXAFS, topografia, cristallografia etc.)".

University of Paris, France.
N. Murray, "The host specificity systems of E. coli".

Max-Planck-Institut für Virusforschung, Tübingen, Federal Republic of Germany.
G. Jürgen, "Zur Genetik des embryoniken Segmentmusters von Drosophila melanogaster".

Max-Planck-Institut für Biochemie, Martinsried/München, Federal Republic of Germany.

K. Simons, "The life cycle of a membrane virus".

August

EMBO and NATO Summer School on "Genome Organization and Function", Spetsai, Greece.
K. Murray, "Prokaryotic cloning vectors" and "Molecular biology of hepatitis virus".
N. Murray, Lecturer.
V. Pirrotta, Lecturer.

September

EMBO-FEBS Laboratory Course on "Molecular Biology of Membranes", Basel, Switerland.
B. Dobberstein, "Structure and biosynthesis of membrane surface antigens".
A. Helenius, "Isolation of membrane proteins".
K. Murray, "Gene cloning in phage lambda vectors" and "Molecular biology of hepatitis virus".
K. Simons, "Structure of membrane proteins".

Max-Planck-Institut, Tübingen, Federal Republic of Germany.
C. Nüsslein-Volhard, "Genetische Analyse der Musterbildung in Drosophila".

Institut d´Immunologie INSERM-CNRS, Marseille-Luminy, France.
D. Louvard, "Mécanismes moléculaires impliqués dans la biogénèse de la surface cellulaire de cellules épithéliales en culture".

European Science Foundation Summer School on "X-ray Scattering with Synchrotron Radiation", Vienna, Austria.
J. Bordas, "Time-resolved x-ray diffraction".
M.H.J. Koch, "The EMBL Outstation at the storage ring DORIS: facilities and scientific program".
J.C. Phillips, "Four circle diffractometry with synchrotron radiation" and "Organic structures".

Herbstschule für Hochenergiephysik, Maria-Laach, Federal Republic of Germany.
H.B. Stuhrmann, "Synchrotronstrahlung und ihre Bedeutung in der molekularbiologischen Strukturforschung".

October

FEBS Course in "Biomolecular Electron Microscopy", Universität Ulm, Federal Republic of Germany.
K. Leonard, Instructor.
P.T. Speck, "Recognition of DNA molecules on electron micrographs: automatic length measurement".

Centre d´Immunologie, Marseille, France.
B. Dobberstein, "Membrane assembly and intracellular transport of histocompatibility antigens".

Department of Genetics, University of Lund, Sweden.
J.-E. Edström, "Control and expression of Balbiani ring genes".

Biology Department, Brookhaven National Laboratory, Upton, NY, USA.
M.H.J. Koch, "Dynamic x-ray diffraction with synchrotron radiation".

EMBO Course on "Membrane Biogenesis", EMBL, Heidelberg, Federal Republic of Germany.
A. Helenius, "Adsorptive endocytosis of Semliki Forest virus".
B.M. Jockusch, "Dynamics of cytoskeletal elements".
D. Louvard, "Use of the MDCK cell line as a model to study cell surface polarity".
D. Meyer, "Studies on the mechanism of vectorial translocation of nascent proteins across the membrane of the rough endoplasmic reticulum".
G. Warren, "The role of the Golgi complex in intracellular transport".

University of Oulu, Finland.
A. Helenius, "How viruses enter cells".

Course on "Methoden und Ergebnisse der Gentechnologie", München, Federal Republic of Germany.
K. Murray, "Phage lambda and cosmids as cloning vehicles" and "Hepatitis B virus and its molecular biology".

November

Department of Cell Biology, Medical School, Yale University, New Haven, Conn., USA.

D. Meyer, "Studies on the mechanism of vectorial translocation of nascent proteins across the membrane of the rough endoplasmic reticulum".

Department of Genetics, University of Wisconsin, Madison, Wisconsin, USA.
D. Byers, "dunce, a mutation of learning and cyclic AMP phosphodiesterase in Drosophila".

Institut de Botanique, Université de Neuchâtel, Neuchâtel, Switzerland.
A. Tsugita, "Development in the analysis of membrane proteins".

Department of Microbiology and Immunology, Albany Medical College, Albany, NY, USA.
D. Meyer, "Studies on the mechanism of vectorial translocation of nascent proteins across the membrane of the rough endoplasmic reticulum".

Department of Cell Biology, Johns Hopkins University, Medical School, Baltimore, Maryland, USA.
D. Meyer, "Studies on the mechanism of vectorial translocation of nascent proteins across the membrane of the rough endoplasmic reticulum",

Biology II, Universität Freiburg, Federal Republic of Germany.
K. Simons, "Semliki Forest virus membrane: a probe for plasma membrane structure and assembly".

Department of Genetics, University of Iowa, Iowa City, Iowa, USA.
D. Byers, "Neurogenetics of learning in Drosophila".

Max-Planck-Institut für Biochemie, Martinsried/München, Federal Republic of Germany.
A. Tsugita, "New strategies for amino acid analysis and sequencing of proteins".

Universität Freiburg, Federal Republic of Germany.
D. Byers, "Natural history of theophilline and caffeine".

Department of Chemistry, University of Virginia, Charlottesville, Va., USA.
D. Meyer, "Studies on the mechanism of vectorial translocation of nascent proteins across the membrane of the rough endoplasmic reticulum".

Department of Physiology and Biophysics, Medical School, University of Southern California, Los Angeles, Calif., USA.
D. Meyer, "Studies on the mechanism of vectorial translocation of nascent proteins across the membrane of the rough endoplasmic reticulum".

Department of Biological Chemistry, University of California, Irvine, Calif., USA.
D. Meyer, "Studies on the mechanism of vectorial translocation of nascent proteins across the membrane of the rough endoplasmic reticulum".

Department of Microbiology, Justus Liebig Universität, Giessen, Federal Republic of Germany.
A. Helenius, "Animal virus entry into cells".

Institut für physiologische Chemie, Ruhr Universität, Bochum, Federal Republic of Germany.
H. Weiss, "Die Struktur von elektronenübertragenden Multienzymkomplexen der Mitochondrienmembran".

Division of Biology, California Institute of Technology, Pasadena, Calif., USA.
D. Meyer, "Studies on the mechanism of vectorial translocation of nascent proteins across the membrane of the rough endoplasmic reticulum".

Department of Microbiology, Medical Center, University of Connecticut, Farmington, Conn., USA.
D. Meyer, "Studies on the mechanism of vectorial translocation of nascent proteins across the membrane of the rough endoplasmic reticulum".

University of Edinburgh, Scotland.
K. Murray, Lecture course on "Recent developments in nucleic acid biochemistry".

Laboratoire de Biochimie, Centre d´Etudes Nucléaires de Grenoble, France.
A. Tsugita, "Recent developments in the analysis of membrane proteins".

Universität Hamburg, Federal Republic of Germany.
H.D. Bartunik, "Zeitaufgelöste Untersuchung biologischer Strukturen und Verwendung der Zeitstruktur der Synchrotronstrahlung".

Universität Hamburg, Federal Republic of Germany.
H. B. Stuhrmann, "Synchrotronstrahlung und neue Methoden der Röntgenstrukturuntersuchung".

EMBL, Grenoble, France.
K. Murray, "Some applications of genetic engineering".

December

Department of Physiology and Anatomy, University of California, Berkeley, Calif., USA.
D. Meyer, "Studies on the mechanism of vectorial translocation of nascent proteins across the membrane of the rough endoplasmic reticulum".

Centre National de la Recherche Scientifique, Strasbourg, France.
B. Dobberstein, "Translocation of proteins across the membrane of the endoplasmic reticulum".

Imperial Cancer Research Foundation, London, England.
A. Helenius, "Virus entry into cells".

Department of Genetics, Universität Düsseldorf, Federal Republic of Germany.
J.-E. Edström, "Function of Balbiani rings".

State University of New York, Buffalo, NY, USA.
J.C. Phillips, "X-ray diffraction and x-ray spectroscopy studies of biological molecules using synchrotron radiation".

Imperial Cancer Research Foundation, London, England.
K. Murray, "Molecular biology versus hepatitis B virus".

Trinity College, Dublin, Ireland.
A. Helenius, "Entry of viruses into eukaryotic cells".

Max-Planck-Institut für Virusforschung, Tübingen, Federal Republic of Germany.
H. Jäckle, "Molecular aspects of normal and experimentally manipulated insect embryogenesis".

Department of Genetics, Universität Hohenheim, Federal Republic of Germany.
R. Tanguay, "Genetic regulation during the heat shock of Diptera".

Department of Genetics, Universität Saarland, Saarbrücken, Federal Republic of Germany.
R. Tanguay, "Genetic regulation during the heat shock response".

Collège de France, Paris, France.
C. Nüsslein-Volhard, "Genetic analysis of segmentation in Drosophila".

National Institute for Medical Research, Mill Hill, London, England.
D.A. Marvin, "Structure and dynamics of filamentous bacterial viruses".

Rockefeller University, New York, NY, USA.
H. Reggio, "Endocytotic pathway of apical membrane proteins in cultured polarized epithelial cells (MDCK)".

Harvard University Medical School, Boston, Mass., USA.
H. Reggio, "Endocytotic pathway of apical membrane proteins in cultured polarized epithelial cells (MDCK)".

Yale University School of Medicine, New Haven, Conn., USA.
H. Reggio, "Endocytotic pathway of apical membrane proteins in cultured polarized epithelial cells (MDCK)".

Rega Institut, Katholieke Universiteit Leuven, Belgium.
H. Garoff, "Structure and assembly of Semliki Forest virus".

University of Edinburgh, Scotland.
N. Murray, "The molecular biology of Type I restriction and modification systems".

University of Bristol, England.
K. Murray, "A molecular biologist's view of hepatitis B virus".

Ernst Boehringer Institut für Arzneimittelforschung, Wien, Austria.
H. Lehrach, "Cloning and sequence analysis of Semliki Forest virus 26S mRNA sequences".

Ain-Shams University, Faculty of Science, Biochemistry Department, Cairo, Egypt.
A. Tsugita, "Protein cleavage in the process of morphogenesis of T4 phage capsid", "Developments in protein sequencing" and "Recent development in protein sequencing for insoluble proteins".

European Science Foundation Instrumentation Subgroup.
J. Bordas, Several meetings during the year as a serving member of the subgroup.

University of Brussels, Belgium.
M. Zabeau, Course of lectures on "Genetic Engineering".

Molecular Biology Unit, Tata Institute for Fundamental Research, Bombay, India.
N. Strausfeld & J.A. Campos-Ortega, Course of lectures on "Neuroanatomy of Drosophila central and peripheral nervous system".

CONTRIBUTIONS AT CONFERENCES, MEETINGS AND SYMPOSIA

January

Biochemical Society Meeting, University of Bristol, England.
K. Murray, "Biological applications of restriction enzymes".

February

7th Aharon Katzir-Katchalsky Conference on "Structural Aspects of Recognition and Assembly in Biological Macromolecules", Nof Ginossar, Israel.
D.A. Marvin, C. Nave, J.E. Ladner, A.G. Fowler, R.S. Brown & E.J. Wachtel, "Macromolecular structural transitions in Pf1 filamentous bacterial virus".
A. Miller, "Collagen structure".

Swiss *Drosophila* Workshop, Bern, Switzerland.
N. Junakovich, C. Tschudi & V. Pirrotta. Poster on "Variability in the molecular organisation of 5S RNA genes among strains of *D. melanogaster*".
G. Scherer, T. Baldari, J. Telford, D. Abildsten, K. Kaiser & V. Pirrotta. Poster on "Cloning of genes differentially expressed during *Drosophila* embryonic development".

Gordon Research Conference on "Structural Macromolecules", Santa Barbara, Calif., USA.
J.C. Jésior, "Crystalline three-dimensional packing is a general characteristic of Type I collagen fibrils".

EMBO Workshop on "Neuronal Development", Simonswald, Federal Republic of Germany.
N.J. Strausfeld, "Aspects of neuropil development in the visual system of the fly".

March

4th Plasmid Mini-Symposium, Bochum, Federal Republic of Germany.
M. Zabeau, K. Breunig, & V. Stirling, "Development of *Eco*R1 z^+m^- plasmids: a new type of cloning vector".

Belgian Biophysical Society Meeting on "Physical Techniques and Mechanisms in Cell Biology", Leuven, Belgium.

G. Warren, "Intracellular transport of membrane proteins".

DECUS München Symposium, Esslingen, Federal Republic of Germany.
P.J. Bendall, Chairman of the session on engineering.

25th Anniversary of the Oholo Biological Conferences on "New Developments of Human and Veterinary Vaccines", Zichron Ya´acov, Israel.
K. Simons, "Effective subunit vaccines against enveloped animal viruses".

ICN-UCLA Symposia on Molecular and Cellular Biology, Keystone, Col., USA.
J. Hosoda, R.L. Burke, H. Moise, A. Tsugita & B. Alberts, "Structural and functional studies of T4 gene 32 helix destabilizing protein".

Hepatitis Conference, Melbourne, Australia.
K. Murray, "Hepatitis B virus genes and their expression in E. coli".

April

Workshop on Elongation, Berlin, Federal Republic of Germany.
B. Antonsson, A. Wittinghofer & R. Leberman, "A simple procedure for the isolation of EF-TU. Some observations.".
D. Suck, W. Kabsch, W.H. Gast & R. Leberman, "Structure of trypsin-modified EF-Tu.GDP from E. coli. A progress report.".

Colloquium der Gesellschaft für Biologische Chemie, "Biological Chemistry of Organelle Formation", Mosbach, Federal Republic of Germany.
T. Bücher, W. Sebald & H. Weiss, Scientific Organizers.
H. Garoff & K. Simons, "The Semliki Forest virus envelope: a probe for studies of plasma membrane and assembly".
K. Simons, "Assembly of animal virus membranes".

Symposium of the British Society for Cell Biology, Liverpool, England.
D. Louvard & H. Reggio, "Insertion and reinsertion of apical membrane proteins occur at the site of the cell to cell contact in epithelial cultured cells from dog kidney (MDCK)".

EMBL Workshop on "Computing and DNA Sequences", Schönau, Federal Republic of Germany.

H. Lehrach, "Cloning and sequencing techniques".
K. Murray, "DNA sequences".

Biochemische Analitik 80, München, Federal Republic of Germany.
K. Murray, "Cloning of hepatitis B virus gene".

May

"Nucleinsaüre in Action", Max-Planck-Institut für medizinische Forschung, Heidelberg, Federal Republic of Germany.
G. G. Kneale, "Gene V-DNA complexes from filamentous phage".
G.G. Kneale, C.W. Gray & D.A. Marvin, Poster on "Isolation and characterization of a nucleoprotein complex from Pf1 infected bacteria".
B. Koller & H. Delius, "Electron microscopic mapping on E. coli and chloroplast DNA".
H. Lehrach, "Cloning and sequence analysis of Semliki Forest virus 26S mRNA".
D.A. Marvin, "Past and future of filamentous phages".
M. Zabeau, K. Breunig & V. Stirling, "Genetic studies of the EcoRI restriction and modification genes".

European Science Foundation Workshop on "Fast Time-resolved Measurements with Synchrotron Light", DESY, Hamburg, Federal Republic of Germany.
R.W. Wijnaendts van Resandt, "Intensity correlation in the picosecond range".

1st International Symposium on "The Biology of Exocrine Pancreatic Cells", Toulouse, France.
V. Herzog & H. Reggio, "Pathways of endocytosis from luminal plasma membrane in rat exocrine pancreas".

Science Research Council Meeting on "Is there a case for a European X-ray Synchrotron Source?", Daresbury Laboratory, England.
J. Bordas, "Advantages of the ESRF for x-ray research".

2nd Mérieux Foundation Conference on "The Pathobiology of Viral Diseases", Lyon, France.
K. Murray, "Cloning hepatitis virus".
K. Simons, "Viral receptors".

FEMS Symposium on "Microbial Envelopes" Saimaanranta, Finland.

A. Helenius, "Virus entry into host cells".

June

Gordon Research Conference on "Biological Regulatory Mechanism", Plymouth, New Hampshire, USA.
C. Nüsslein-Volhard, "Segmentation in Drosophila.

Nordic Symposium on "Research with Synchrotron Radiation in Physics, Chemistry and Biology", Gysinge, Sweden.
J. Bordas, "Time-resolved radiation and anomalous dispersion".
H.B. Stuhrmann, "Synchrotron radiation and anomalous dispersion".

1st European Bioenergetics Conference, IUB-IUPAB Bioenergetics Group, Urbino, Italy.
K. Leonard, T. Arad, P. Wingfield & H. Weiss, "Three-dimensional image reconstruction of cytochrome c reductase from Neurospora mitochondria".
H. Weiss, P. Wingfield, K. Leonard, F. Winkler, S. Perkins & A. Miller, "Structure of ubiquinone: cytochrome c reductase from Neurospora mitochondria".

20e Colloque Annuel de la Société Française de Microscopie Electronique, Poitiers, France.
J.-C. Homo, "Un microcryosystème pour les STEM et TEM à haute résolution".
J.-C. Jésior, "Arrangement moléculaire des fibrilles de collagène: une étude combinée par diffraction X et microscopie électronique".

28e Congrès International de Physiologie, Budapest, Hungary.
D. Louvard, "Molecular mechanisms in development of cell surface specialisations as displayed by epithelia".

Juselius Foundation Symposium on "Expression of Eukaryotic Viral and Cellular Genes", Helsinki, Finland.
H. Garoff, "Structure and biogenesis of the Semliki Forest virus membrane".

5th Munich Symposium on Microbiology, Munich, Federal Republic of Germany.
A. Helenius, "Mechanisms of virus entry into host cells".

The Planning Group for Lipolytic Enzymes, Swedish Natural Research Foundation, Falstabo, Sweden.

A. Helenius, "How do viruses enter into animal cells?".

Gordon Research Conference on "Nucleic Acids", New Hampton, New Hampshire, USA.
H. Lehrach, "Cloning and sequencing techniques".

July

EMBO Workshop on "Protein-DNA Interactions in Bacteriophages", Salamanca, Spain.
N.E. Murray, "The hsd region of E. coli analysed in lambda-transducing phages".
M. Zabeau, K. Breunig & V. Stirling, "Genetic studies of the EcoRI restriction and modification genes".

Symposium on tRNA, Strasbourg, France.
R. Cortese, G. Ciliberto, L. Castagnoli, J. Jonkman & D. A. Melton, "Expression of tRNA genes".

Gordon Research Conference On "Lysosomes", Procton Academy, New Hampshire, USA.
A. Helenius, "Role of lysosomes in virus penetration".

Gordon Research Conference on "Animal Cells and Viruses", Tilton, New Hampshire, USA.
H. Garoff, "Structure and assembly of Semliki Forest virus".

ECM-6, Barcelona, Spain.
H.D. Bartunik and K.S. Bartels, "Macromolecular crystallography with synchrotron radiation: high resolution and low temperature studies".
J. Bordas and M.H.J. Koch, "Time-resolved small-angle x-ray diffraction and scattering from biological structures with synchrotron radiation".
M.H.J. Koch, Organizer of the session on "Synchrotron Radiation in Biology".

Gordon Research Conference on "Diffraction Methods in Molecular Biology", Andover, New Hampshire, USA.
H.B. Stuhrmann, "Time-resolved solution scattering at DORIS".

4th International Meeting on Immunology, Paris, France.
S. Kvist, K. Wiman, P.A. Petersen & B. Dobberstein, "Biosynthesis and intracellular transport of the HLA-DR antigen".

August

EMBO Workshop on "Stereochemical Mechanisms in Allostery", King's College, Cambridge, England.

M.F. Moody, A.M. Foote & P. Vachette, Poster on "Allosteric transition of aspartate transcarbamylase" in collaboration with K. Bartels, H. Bartunik, J. Bordas, A. Gabriel, M. Koch, J. Phillips, S. Provencher, A. Tardieu & F. Winkler.

Drosophila Workshop, Colymbari, Crete, Greece.
C. Nüsslein-Volhard, "Embryonic lethals in Drosophila".

4th Arolla Workshop on "Formation of Messenger RNA in Eukaryotic Cells", Arolla, Switzerland.
J.-E. Edström & H. Sierakowska, "Balbiani ring translation products and control of their formation".

7th European Congress on Electron Microscopy, The Hague, The Netherlands.
R. Freeman, F. Booy & K. Leonard, "Cold transfer and observation of frozen hydrated specimens in the scanning transmission electron microscope".
R. Freeman, K. Leonard & J. Dubochet, "The temperature dependence of beam damage to biological samples in the scanning transmission electron microscope".
J.-C. Homo, "Micro-cryostat for high resolution electron microscope specimen stage".
J. Lepault & J. Dubochet, "Preservation of biological specimens".
A.J. Pitt, "The WPO image of $Ti_2Nb_{10}O_{29}$ as a member of resolution".
P.T. Speck, "Automated recognition of line structures or noisy raster images applied to electron micrographs". (This talk was also given in High-light Session of the Conference.)

Meeting on "SV40-adenovirus", Cold Spring Harbor, NY, USA.
H. Maner, A. Neer, M. Zabeau & N. Boran, "Cloning of chromosomally associated polyoma virus DNA from an inducible line of polyoma virus-transformed cell line in a lambda bacteriophage vector".

13th FEBS Meeting, Jerusalem, Israel.
L. Dente, E. Ullu, K. Goldman, I. Bossom & M. Melli, "Human histone genes".
V. Pirrotta, "Cloning of Drosophila genes active during embryogenesis".
K. Simons, "Assembly of the Semliki Forest virus membrane".
D. Suck, W. Kabsch, W.H. Gast & R. Leberman, "X-ray structure analysis of E. coli elongation factor Tu".
J. White & A. Helenius, Poster on "Membrane fusion activity of Semliki Forest virus".

September

2nd International Congress on Cell Biology, Berlin, Federal Republic of Germany.
G. Darai, L. Zöller, B. Matz, R. M. Flügel, H. Gelderblom, P. T. Speck & H. Delius, "A rapid method for differentiation of mycoplasmas using DNA restriction enzymes".
B. Dobberstein, "Membrane assembly and intracellular transport of histocompatibility antigens".
A. Helenius, J. White & M. Marsh, "Are lysosomes the site of virus penetration into animal cells?".
B.M. Jokusch, B.A. van Oost & F.G.I. Jennekens, "Congenital nemaline myopathy: an inherited disorder characterised by an abnormal distribution of the Z-line protein, alpha actinin".
M. Marsh & A. Helenius, "Adsorptive endocytosis of Semliki Forest virus".
K. Matlin, H. Reggio, K. Simons & A. Helenius, "The entry of Fowl Plague virus into MDCK cells".
H. Reggio & D. Louvard, "An apical membrane protein, aminopeptidase, appears at the site of cell to cell contact in a culture of kidney epithelial cells".
R. Tanguay, "Intracellular distribution of heat shock induced proteins in Diptera".

4th European Neuroscience Meeting, University of Sussex, Brighton, England.
G. Geiger & D.R. Nässel, Poster on "Correlation between neuropil structure and visual behaviour of the fly Musca domestica".

DECUS Europe Symposium, Amsterdam, The Netherlands.
P.J. Bendall, Chairman of the session on "Alternatives to RT-11".

6th EMBO Annual Symposium, EMBL, Heidelberg, Federal Republic of Germany.
H. Delius, "Heteroduplexes between E. coli and chloroplast ribosomal DNAs".
K. Murray, "Molecular biologists look at green plants".

16th Harden Conference on "Microtubules and Microfilaments: Structure and Function", Wye College, Kent, England.
B.M. Jockusch, "Alpha actinins: their role in organizing microfilaments".

Colloquium der Gesellschaft für Biologische Chemie, "Structure and function of HD+U-transducing membrane proteins, " Reisensburg, Günzburg, Federal Republic of Germany.

H. Weiss, "Structure of mitochondrial ubiquinone: cytochrome c reductase".

EMBO Workshop on "Regulation in Prokaryotes and Other Simple Organisms", Rome, Italy.
V. Pirrotta, "An unusual promoter in the lambda immunity region".

35th Symposium of the Society for Experimental Biology. Eukaryotic and Prokaryotic Flagella. Cambridge, England.
D.A. Marvin, participant.

Annual Meeting of the Italian Society of Biological Chemistry, Bologna, Italy.
G. Ciliberto, L. Castagnoli, D.A. Melton & R. Cortese, "Espressione dei geni del tRNA".

European Symposium on "Connective Tissue Research", Prague, Czechoslovakia.
C. Berthet-Colominas, "Structural studies of collagen in cartilage".
A. Miller, "Three-dimensional structure of collagen".

14th International Embryological Conference, Patras, Greece.
E. Wieschaus, "Maternal effect mutations and the establishment of embryonic pattern in Drosophila" and "The role of compartments in the development of Drosophila".

British Association for the Advancement of Science, Manchester, England.
K. Murray, "Genetic engineering and its applications in biomedical science".

October

Elektrophoresis Forum, München, Federal Republic of Germany.
W. Ansorge, "Verfahren und Vorrichtung zur Herstellung von sehr dünnen (0,02-1,5 mm) Gelen und ihr Anwendung auf DNA-Sequenzierung, Proteintrennung mit Silberanfärbung".

Deutsche Forschungsgemeinschaft Colloquium, "Membrane Proteins: Analysis of Molecular and Supramolecular Structure." Maria Laach, Federal Republic of Germany.
H. Weiss, "Mitochondrial electron transfer enzymes: resolution and reconstruction of 3-D structures".

Annual Meeting of the Italian Genetics Society, Alghero, Italy.

L. Castagnoli, G. Ciliberto, D.A. Melton & R. Cortese, "Espressione dei geni del tRNA".

XVII Congresso Nazionale della Società Italiana di Biofisica, Como, Italy.
G. Cesarini, "A new vector for recombinant DNA with direct selection for DNA fragments of 20kb".
R. Cortese, G. Ciliberto, G.L. Castagnoli and D.A. Melton, "Espressione dei geni del tRNA".

Congresso della Società Italiana di Biologia della Riproduzione e dello Sviluppo, Como, Italy.
E. Ullu, "Organization of repeated sequences in the human genome".

5e Colloque Annuel du Cercle Français de Biologie Cellulaire, Institut Pasteur, Paris, France.
D. Louvard, "Participation des protéines du cytosquelette à la dynamique des membranes".
H. Reggio & D. Louvard, "Une protéine de la membrane apicale apparait dans la région des contacts cellulaires dans une lignée de cellules épithéliales"

International Conference on "Small-Angle Scattering", Berlin, Federal Republic of Germany.
J. Bordas, "Time-resolved x-ray scattering of tubulin".
S. Cusack, "Neutron scattering studies of the structure of Alfalfa Mosaic virus".
B. Jacrot, "Neutron small-angle scattering in biology".
H.B. Stuhrmann, "Synchrotron radiation".

Opening of the SSRL Biotechnology Resource Centre, Stanford, Calif., USA.
M.H.J. Koch, "Biological applications of dynamical small-angle scattering and diffraction".

Conference de la Société Franç aise de Physique, Paris, France.
B. Jacrot, "Virus structure and morphogenesis".

November

Annual Meeting of the Swedish Biochemical Society, Uppsala, Sweden.
B. Dobberstein, "Biosynthesis and secretion of eukaryotic proteins".

ESF-EMBL-CNRS Meeting on "X-ray Detectors for Synchrotron Radiation", Hamburg, Federal Republic of Germany.
H.D. Bartunik, "General requirements for protein crystallography" and "Rapid data handling system using frame selection by hardware for time resolved diffraction experiments with an area detector".
J. Bordas, Co-organizer of the meeting with R. Fourme.
C. Boulin, "Fast data acquisition systems for linear and bidimensional x-ray detectors".
E. Dorrington, "Time frame generator: device to enable time-resolved data acquisition".
P. Gill, "Design of electronics for address generation in multiwire chambers".
J. Hendrix, "A novel detector system with high spatial resolution and high counting rate capability".
M.H.J. Koch, "Requirements for detectors and data acquisition systems for time-resolved measurements".
H.B. Stuhrmann, "Some practical aspects of the use of a Gabriel area counter as collected since 1977".

December

British Biophysical Society Meeting on "Nucleic Acids: Interactions with Drugs and Carcinogens", Imperial College, London, England.
D.A. Marvin, participant.

SEMINARS

R. Jaenicke (Regensburg)	Faltung und Assoziation Oligamerer Proteine
B. Geiger (Rehovot, Israel)	The involvement of a new smooth muscle protein vinculin in the association of microfilaments with the cell membrane
L. Bossi (Salt Lake City, USA)	Codon reading by transfer RNA is affected by mRNA sequence adjacent to the codon
L. Sachs (Rehovot, Israel)	Uncoupling of the controls for growth and differentiation in leukemia: a general model for the origin of malignancy
M. Breitenbach (Vienna)	The role of the mitochondrial genome in yeast sporulation
B. Povh (Heidelberg)	Proton microprobe for the elemental analysis of biological samples
V. Herzog (Munich)	Pathways of endocytosis in thyroid epithelial cells
T. Otzuka (Cambridge)	Excision of intervening sequences in tRNA by RNase XL 1
G. Piperno (New York, USA)	Genetic and biochemical approaches to the study of eukaryotic flagella
A. Tartakoff (Geneva)	Intracellular transport of immunoglobulin M
A. Lewit-Bentley (Grenoble)	Low-resolution neutron crystallography of the nucleosome core particles

Y. Courtois (Paris)	Phenotypic modification and stimulation of lens epithelial and corneal endothelial cells induced by a new eye derived growth factor
W. Bode (Martinsried)	Structural and spectroscopic investigations of the trypsinogen - trypsin system
K. Timmis (Berlin)	Control of plasmid replication
T. Wakabayashi (Tokyo, Japan)	Three-dimensional image analysis of muscle thin filament
Nam-Hai Chua (New York, USA)	Energy-dependent transport of proteins into chloroplasts
J. Schlessinger (Rehovot, Israel)	Significance of motion and clustering in the mode of action of peptide hormones
A. Hinnen (Basel)	Yeast transformation and the isolation of yeast genes
G. Kreibich (New York, USA)	Structural and functional studies on liver rough microsomes
J. Hall (Waltham, USA)	Love and death in neurotransmitter mutants of <u>Drosophila</u>
R. May (Grenoble)	New strategies for the structure determination of complex macromolecules
K. Howell (New Haven, USA)	Heterogeneity of golgi elements
D.P. Leader (Glasgow)	Phosphorylation of eukaryotic ribosomal proteins

J.D. Jamieson (New Haven, USA)	Surface properties of differentiating and dedifferentiating pancreatic acinar cells: possible interrelationship
M. Hofnung (Paris)	Membrane protein positioning in E.coli K12
G. von Heijne (Stockholm)	Trans-membrane translocation of proteins
M. Nomura (Madison, USA)	Feedback regulation of ribosome protein gene expression in E.coli
T. Roth (Lausanne)	Coated vesicles: a carrier for protein transport
J. Finne (Basel)	The ABH antigens of erythrocytes: a model for membrane carbohydrates
H.Rose (Darmstadt)	Prospect of high resolution electron microscopy
K. Hodgson (Stanford, USA)	Molecular structure in biological systems studied by synchrotron radiation: EXAFS and anomalous scattering studies
W.N. Lipscomb (Cambridge, USA)	How do enzymes work?
J. Broach (New York, USA)	Replication and recombination functions encoded by the yeast plasmid 2μ circle
H. Uchida (Tokyo, Japan)	Initiation of DNA replication in a col E1-type replication
M. Johnston (Salt Lake City, USA)	The regulation of the histidine operon in salmonella typhimurium

P.M. Bhargava (Hyderabad, India)	Regulation of cell division and malignant transformation through control of the uptake of essential nutrients
M. Grütter (Eugene, USA)	Structure, function and stability of native and mutant T4 phage lysozymes
D. Kemp (Melbourne, Australia)	Alternative 5′ and 3′ splicing of immunoglobin Cμ RNA transcripts in T and B lymphocytes
I. Mellman (New York, USA)	Endocytosis and the F_c-receptor
M.J. Gething (London)	Cloning and DNA sequence of influenza virus hemagglutinine and matrix protein genes
P. Southern (Stanford, USA)	Simian Virus 40 vector systems
D. Tsernoglou (Detroit, USA)	Structure and function of snake venom neurotoxin
M. Blumenfeld (St. Paul, USA)	Control of chromatin condensation during the development of Drosophila
L. Gerace (New York, USA)	The nuclear lamina and the structural organization of the nuclear envelope
L.A. Feigin (Moscow, USSR)	Some recent results on the structure of viruses from small-angle scattering experiments and refined data analysis
J. Rothman (Stanford, USA)	Intracellular transport of the vesicular stomatitis viral glycoprotein
E. Trifonov (Rehovot, Israel)	Sequence dependent bendability of DNA and the mapping of nucleosomes

T. Mulvey (Birmingham)	High resolution electron microscopy - instrumentation and applications
L. Philipson (Uppsala)	Adenovirus gene expression - from molecular morphology to control mechanism
U. Schmeissner (Bethesda, USA)	Transcription of the integrase gene in bacteriophage λ
J.S. Emtage (High Wycombe)	Genetic manipulation of influenza and interferon genes
V. Colantuoni (New York, USA)	Amplification of viral genomes in polyoma transformed rat cells
A. Ullrich (San Francisco, USA)	Interferon genes and their expression
W.H. Elliott (Adelaide, Australia)	Is there a different type of mRNA for extracellular enzymes in prokaryotes?
F.R.N. Gurd (Bloomington, USA)	How individual charged groups function at the aqueous-nonpolar interface: implications for simple proteins, molecular aggregates and membranous systems
A. Kaji (Philadelphia, USA)	A drug resistance factor Rts1 - a unique plasmid with various host effects which include temperature sensitive restriction of T4 phage and thermosensitive host growth
D. Shugar (Warsaw)	Recent progress in development of antiviral agents
F. Quiocho (Oxford)	Structure and function of binding proteins for active transport and chemotaxis in bacteria

J. Ofengand (Nutley, USA)	Arrangement of the donor and acceptor tRNAs on the E.coli ribosome as studied by photoaffinity labelling
M. Smith (Edinburgh)	The histone genes of saccharomyces cerevisiae
H.L. Monaco (Padova)	Crystal structure of aspartate transcarbamylase to a nominal resolution of 2.8 Å
G. Isenberg (Munich)	News about actin as a structural and energy transducing molecule in non-muscle and neuronal cell motility
H. Heumann (Martinsried)	Study of the quarternary structure of DNA-dependent RNA polymerase with neutron and x-ray small-angle diffraction
H. Frauenfelder (Urbana, USA)	Dynamic protein structure
K. O'Hare (Strasbourg)	SV40 and Polyoma derived vectors for expression of DNA sequences in eukaryotic cells
O.L. Miller, Jr. (Charlottesville, USA)	Ultrastructural aspects of genetic activity
D.A.M. Mesland (Amsterdam)	Membrane-associated cytoskeleton and coated vesicle formation in cultured hepatocytes visualized by dry-cleaving
E. Remaut (Gand)	A family of expression vectors using lambda's P_L promoters
E. Fries (Stanford, USA)	Active transport of membrane glycoprotein in the golgi complex

D. Dorset (Basel)	Electron crystal structure analysis of biological molecules
M. van Heel (Groningen)	Structure of biological macromolecules by multivariate statistical analysis of electron images
J. Mauchamp (Marseille)	Environmental factors involved in the orientation of epithelial cell polarity in culture: the thyroid epithelial
P. Schedl (Princeton, USA)	Chromatin structure of active genes
W.O. Saxton (Cambridge)	Lattice averaging over distorted crystals applied to the HPI layer of the cellwall of Micrococcus radiodurans
W. Schaffner (Zürich)	High expression in HeLa cells of genomic rabbit globin DNA linked to SV40 DNA
W. Hennig (Nijmegen)	Functions of the Y-chromosome during spermatogenesis of Drosophila hydei

LECTURES

W.N. Lipscomb (Cambridge, USA)	How enzymes work
R.L. Gregory (Bristol)	Perceptions as hypotheses
F. Jacob (Paris)	On the first days of the mouse embryo
T.H. Jukes (Berkeley, USA)	Silent nucleotide substitutions in evolving genes
F. Crick (San Diego, USA)	Selfish DNA
M. Eigen (Göttingen)	Experiment on biogenesis
S. Tonegawa (Basel)	Somatic reorganization and diversification of immunoglobulin genes
V. Luzzati (Gif-sur-Yvette)	The structure of low density serum lipoprotein