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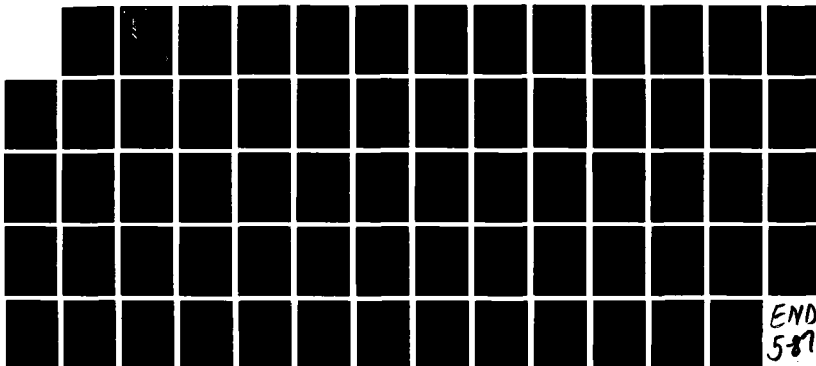
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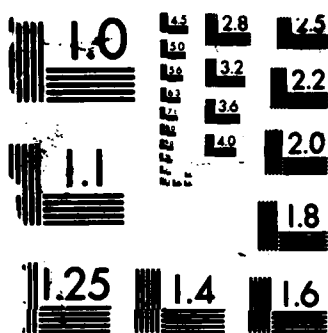
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Behavioral Sciences

- Canth L.P.A. → Norway's Center for Disaster Psychiatry
A Unique Institution for the Study and
Treatment of Victims of Catastrophe William D. Crano 227

Studies at the Center for Disaster Psychiatry dealing with posttraumatic stress disorder (PTSD) have covered survivors of Nazi concentration camps, sailors subjected to years of extreme and unrelieved stress, and victims of a large-scale industrial accident. This and other work of the center represents some of the best longitudinal research on the psychological effects of long-term stress and, in the author's view, serves as a model of what research in the area can be.

Biological Sciences

- Molecular Biology: Eukaryotic
Chromosome Replication Claire E. Zomzely-Neurath 230

Topics of this meeting in London, UK, in December 1986 included chromosome structure and gene replication, viral models for eukaryotic DNA replication, selective protein turnover, or, mitochondrial DNA replication, initiation of DNA replication in yeast chromosomes, and the effect of inositol lipids on DNA synthesis. The author summarizes the presentations.

- Molecular Biology: Conference on Genetic
Engineering Techniques Claire E. Zomzely-Neurath 235

Selected presentations given at this seminar, held in November 1986 at London, UK, are summarized. The scientific program comprised the following sessions: isolation of large segments of chromosomal DNA, cloning and expression in *E. coli*, expression in mammalian cell culture and transgenic mice, and engineering specific genes.

- Bioelectrochemical Symposium, Formations
and Reactions of Peroxides in
Biological Systems Claire E. Zomzely-Neurath 239

The basis for this conference was the evidence of studies indicating the importance of peroxides formation in biochemistry, physiopathology, and pharmacology. The interdisciplinary aspect of the research in this area was emphasized by the attendance of chemists, biophysicists, and researchers in medical fields.

- Biotechnology: Conference on Large-Scale Production of Monoclonal Antibodies ;..... Claire E. Zomzely-Neurath 244**

Topics of this conference, held in London, UK, in December 1986, included production of monoclonal antibodies (Mabs) in airlift reactors, immobilized cell culture systems, antibody production in cell cultures, and factors affecting hybridoma viability. Presentations in these topics are summarized.

Material Sciences

- Crystal Growth Under Microgravity Conditions ;..... Louis Cartz 249**

The growth of crystals from solution under gravity and microgravity is reviewed. Turbulent convection currents affect crystalline perfection. Methods to reduce convection currents involve using isodensity systems, increasing the viscosity, using special configurational arrangements, or microgravity. Some alloy systems such as Mn-Bi and Ga-Hg have miscibility gaps which can give rise to macrosegregation effects under gravity. These effects can be overcome under microgravity conditions.

- The French Society of Metallurgy ;..... Louis Cartz 253**

Subjects discussed at the meeting of the Société Française de Métallurgie included quasi-crystalline solids and ion beam mixing. An extensive review is given of the treatment of metals by high-energy beams of ions, lasers, and electrons, when surfaces can undergo structural modifications or changes in composition resulting in modified surface properties.

Mechanics

- First International Symposium on Domain Decomposition Methods ;..... Eugene F. Brown 256**

This conference, held in Paris in January 1987, brought together computer scientists, engineers, mathematicians, and physicists to discuss the theoretical and practical aspects of applying domain decomposition methods. The author comments on progress concerning the application of domain decomposition methods to finite element, finite difference, finite volume, and spectral methods.

Physics

- ONR Branch Office London Sponsors a Session on Interfacial Phenomena in Microelectronics ;..... Paul Roman 259**

Four talks presented at a special session on interfacial phenomena in microelectronics are reviewed. This session was organized within the framework of a Europhysics Summer School on Physicochemical Hydrodynamics and Liquid State Conference at Rabida, Spain, July 1986. Theory of solidification, layered semiconductor structures, and crystal growth under microgravity were the topics of these ONRL-sponsored presentations.

Optical Communication Conference, Draws Crowds to Barcelona	Paul Roman	261
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The 12th European Conference on Optical Communication (ECOC) took place in Barcelona, 21 through 25 September 1986. Apart from a general overview, this article reports in some detail on contributions in the areas of semiconductor lasers, integrated optics, nonlinear optics, and optical switching.

Space Sciences

NATO Advanced Study Institute--Physical Processes in the Interstellar Medium	Philip R. Schwartz	265
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Topics at the meeting included the structure and distribution of molecular clouds; cloud cores and nearby clouds; triggered star formation; chemistry, dust, and dust formation; and magnetic fields. Presentations on these topics are reviewed.

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Behavioral Sciences

NORWAY'S CENTER FOR DISASTER PSYCHIATRY: A UNIQUE INSTITUTION FOR THE STUDY AND TREATMENT OF VICTIMS OF CATASTROPHE

by William Crano. Dr. Crano is the Liaison Scientist for Psychology in Europe and the Middle East for the Office of Naval Research's London Branch Office. He is on leave until June 1988 from Texas A&M University, where he is a Professor of Psychology.

How people cope with extreme stress is one of psychology's continuing preoccupations. Recently, I reported on a NATO conference whose central theme was the human response to catastrophic events (ESN 41-4:175-178). At that conference, Professor Lars Weisaeth (Oslo, Norway) presented some intriguing research that he and his group conducted on the victims of a major avalanche which occurred during a NATO training exercise in Norway. A follow-up meeting with Weisaeth provided additional information about his unique institution, Norway's Center for Disaster Psychiatry. The Center is associated with the University of Oslo, and is part of the Psychiatric Institute of Gaustad, in Oslo. In this report I will describe the beginnings of the Center and the results of some of the group's ongoing research.

The Eitinger Tradition

Long before the term "posttraumatic stress disorder" (PTSD) was popular, Leo Eitinger, the father of Norway's Center for Disaster Psychiatry, was dealing with the Norwegian survivors of Nazi concentration camps, and with Norwegian sailors who, for 5 years during the second World War, had worked under conditions of unremitting danger and stress. Eitinger's work (see Eitinger and Strom, 1973, for an English description) represents some of the best longitudinal research on the psychological effects of long-term stress. I will describe some of this research as a means of providing background for the Center, a unique and valuable institution which has produced some remarkable research on the effects of long- and short-term stress, and the psychological and physical outcomes of those who endure it.

Background: The Concentration Camp Survivors. The story begins during the grim days following the end of the second World War. Immediately after the war,

Norway (and only Norway) assembled a complete register of all of the country's citizens who had been incarcerated by the Nazis. With this information, it was possible to compare the mortality and morbidity rates of Norwegian concentration camp victims with those of the general population. To their credit, the Norwegians have followed this group up to the present day, frequently comparing their physical and psychological status with that of the general population. The outcomes of these comparisons are far from pretty. As late as 40 years after their liberation, concentration camp victims have a higher mortality rate than nonprisoners. The victims have been shown to be less successful in their work, to have moved more frequently, taken more sick leave (and of longer duration) and to have been hospitalized more often than the (age-matched) population at large. Remarkably, the frequency of psychosis among survivors was 5 to 10 times higher than that of the general population during the first 10 years after the war.

This finding is doubly interesting given the historical context in which it was developed because, contrary to theory-based expectations of the immediate postwar period, the psychiatric problems of the survivors did not present themselves immediately. By the end of 1946, for example, very few concentration camp survivors were registered as war casualties in need of (psychiatric) disability pensions. Only later--sometimes much later--did the debilitating effects of the camp experience emerge. Eitinger's data comprehensively established the existence of a latency period, which intervened between the cause of a psychiatric difficulty and its behavioral expression. Before this work, such a possibility would have been thought implausible. Eitinger's study demonstrated that concentration camp victims were much more likely than an average Norwegian comparison sample to suffer organic and reactive (stress-produced) psychoses. To explain this difference, Eitinger showed that the victims who eventually did "break down" were likely to have suffered torture, head injuries, massive weight loss, and extreme, persistent, fear during their captivity. These physical and psychological traumas must be at least partially responsible for the observed higher frequency of organic and reactive psychoses in the concentration camp population.

Background: The Norwegian Sailors. During 1942-43, on average, one Norwegian ship was torpedoed every third day. These ships typically carried exceptionally volatile cargoes--gasoline, explosives, ammunition. Many Norwegian sailors crewed these ships without interruption for

5 years, under conditions of inhuman stress. They could not avoid the danger nor flee from it. Indeed, they could not even defend themselves against those who were responsible for the threat to their lives. Though the sailors suffered no physical torture at the hands of their Nazi captors (as did the concentration camp victims), they were under almost constant attack from Allied submarines and airplanes, frequently deprived of sleep for extended periods and, sometimes for years on end, unable to communicate with loved-ones, who did not know if they were alive or dead. It is little wonder, then, that one-third of the survivors tested in this crucible were psychologically disabled. What is remarkable is not that this percentage is so high, but that it so low in light of the stresses suffered by the sailors. Equally remarkable is the latency of psychopathological onset: for some of the survivors, problems did not surface until the 1970's! The PTSD-related difficulties of the sailors resemble those of the concentration camp survivors over the life-span; like the survivors, the sailors proved to be much more susceptible than the general population to somatic, psychosomatic, and psychiatric difficulties, and to be less successful in their work; in brief, to have led emotionally impoverished, unrewarding lives.

Today's Center

Sensitized to the problems of catastrophic events on the population at large, the Norwegian authorities established the Center for Disaster Psychiatry, whose combined charge is to offset the negative psychological effects of any catastrophic event that befalls a Norwegian citizen, and to study the individuals involved in such events to learn more about human responses to extreme stress, catastrophe, etc. In retrospect, this was a wise, perhaps necessary decision, since in a country with a limited population, as Norway, a major catastrophe is likely to touch a much greater proportion of the country's citizenry. From experience, we know that the demands of treatment and of research are often less than completely compatible. However, under Eitinger and later Weisaeth, the Center appears to have come to a very healthy accommodation of these sometimes conflicting goals. In Weisaeth's view, victims of catastrophes will participate in research if they feel that by doing so, they are being helped, and that they are helping others. So, the researcher in this area must offer a quid pro quo if he or she is to succeed in maintaining clients' cooperation. The proof of the utility of this approach can be seen in

Weisaeth's minuscule drop-out rate; in some of his longitudinal studies, carried out over 5-10 years, the complete sample is maintained.

A brief discussion of some of the treatment-research undertakings in which the Center has been involved will provide some understanding of the realm within which Weisaeth's group operates and the kinds of useful psychological information it can produce. In some important ways, the thrust of the Center today has been expanded from that of Eitinger, whose early work was primarily retrospective in nature, focused as it was on the reconstruction of events and circumstances that gave rise to the manifest psychological or physical problems. In today's Center, Weisaeth and his group study disaster victims' responses as close in time to the disaster as they can, and follow longitudinally the course of responses to extreme stress. In addition, they compare those disaster victims who suffer from PTSD with those who do not, in order to isolate personal and situational factors that might produce greater or lesser vulnerability to stress.

The Industrial Accident

A good example of the expanded orientation is available in the Center's research on the victims of a major industrial accident which occurred in Norway's largest paint production plant. As a result of an accidental explosion, the entire factory was destroyed. Thirty thousand square meters of buildings were consumed by a fire which, at its height, reached 1200 feet. The fire was brought under control after 36 hours. Remarkably, there were only six fatalities; two of the 125 survivors suffered severe injury, and another 21 had minor injuries. Psychiatric assistance was provided all workers almost before the ashes cooled.

In addition to the provision of treatment, research on the survivors began immediately. For purposes of the study, survivors were divided into three groups:

- Those who were in the immediate vicinity of the explosion (the extreme risk group, 66 workers)
- Those in the factory at the time of the explosion, but some distance from it (the moderate risk group, 59 workers)
- Employees of the company who were off-duty at the time of the explosion (low risk group, 121 workers).

Proximity to the life-threatening event clearly had an impact on the likelihood of adverse psychological reaction: 42.1 percent of those in the extreme risk group showed severe, marked, or moderate

degrees of PTSD 1 week postexplosion, as compared with 22.1 percent of the moderate risk group, and 9.7 percent of the low risk group. Seven months later, the percentages were 36.4 percent, 17 percent, and 4.1 percent, for the extreme, moderate, and low risk groups, respectively. The severity of workers' early response at 1 week postdisaster predicted their status at 7 months with a sensitivity of 0.96, and a specificity of 0.89.

Seven months appears to be an important time-marker. Longitudinal research showed that those who had not been able to move out of the "severe" PTSD category at 7 months were destined to remain there over the 3-year time span of the study. Delayed PTSD reactions were almost nonexistent. In conjunction with other research from the Center, this result seems to suggest that delayed stress reactions are not likely following brief traumas; a long, intense stress experience appears to be required before delayed reactions occur.

What Influenced Pre- and Postdisaster Behavior? Research was undertaken to determine whether the adequacy of workers' behavior in response to the catastrophe could be predicted on the basis of information available before the event. Briefly, "disaster behavior" was trichotomized as optimal (i.e., helping oneself and others to escape to safety), adequate (helping oneself), and inadequate ("freezing," or uncontrolled flight behavior). Personality tests, attitude scales, and socio-demographic information was (or had been previously) collected and used to differentiate workers in terms of disaster behavior. A number of variables correlated positively with more optimal responding. In general, those who responded best in the disaster were males over 40 years of age, with a strong company identification, a realistic threat appraisal, low psychosomatic reactivity, low-state anxiety, high intelligence, previous disaster training or exposure, a maritime background (earlier, fishing had provided the principal livelihood of many of the company town's inhabitants), and position of responsibility.

While all of these factors mattered, the variable that had the greatest predictive power was prior disaster training or exposure. In a discriminant function analysis, this variable correctly predicted with 84 percent accuracy whether the worker would display optimal or suboptimal disaster behavior. The importance of prior experience/training was such that 67 percent of those with prior disaster training reacted optimally to the disaster, and the remainder of this group responded adequately. None exhibited sub-

optimal disaster performance. At the other extreme, no one with little training or experience responded optimally in the disaster, and 50 percent of this unprepared group reacted inadequately.

Equally important, there was a negative association between adequacy of disaster behavior and the likelihood of PTSD. Those who behaved well in the emergency were less likely to suffer post traumatic shock. This is an interesting finding, since it implies that we can lessen the likelihood of PTSD by prior training. The finding suggests that susceptibility is not a function of variables that are difficult or impossible to manipulate, like sex, intelligence, age, etc., but rather that susceptibility might result from a lack of preparedness. The implications of such a possibility could prove extremely important.

A significant methodological postscript to this research is that the dropout rate in this study was 0 percent. This is important, since the 16 percent who proved most resistant to the initial examination--but who eventually cooperated--accounted for 38 percent of the PTSD group after 7 months. Resistance, then, was a characteristic of the high-risk group. Weisaeth observes that if an apparently respectable response rate of 80 percent had been obtained, perhaps 40 percent of the most severely disturbed workers would have been missed. This finding and observation should serve as important advice for workers in this area.

Other Projects at the Center

Other projects that have occupied the energies of the Center's staff include a study of the coping behaviors and psychological aftereffects of a group of 14 Norwegian sailors who in 1984 were taken prisoner by Libya and held (and tortured) for 67 days. Research continues with these men, but the intermediate findings are intriguing. As might be expected, typical reactions to the torture were fear and depression. However, rage, too, was a common response. Control of rage was crucial, since its expression could result in even more severe maltreatment. Behavioral control of the rage reaction, however, while necessary, caused later psychological problems. Techniques of coping used by the men to survive their ordeal included an increase in group cohesion, physical activity to avoid reality, the search for a deeper meaning of the encounter, the psychological reduction of the captors, religious faith, daydreams, and fantasy. These techniques apparently helped the men survive the immediate threat: none of the seamen admitted to the Libyan charges of

spying, despite the fact that one was killed, and others tortured in view of their comrades in arms. However, seven of the 13 survivors suffered PTSD, and were still in treatment 6 months after their release.

Norwegian soldiers assigned a peace-keeping role in Lebanon for the United Nations provide yet another group of potential PTSD victims studied by the Center. Norway provided four contingents of 650-660 soldiers to this force. Each group served for 6 months in Lebanon, and 10-15 percent of each group volunteered for another tour of duty. Weisaeth served as the psychiatrist for the first two Norwegian contingents, and as such, had the opportunity to observe the interplay of stress and coping at first hand. In his description of the work undertaken in this setting, one observation is particularly insightful, and deserves repeating. In Weisaeth's words, the fundamental cause of PTSD in the UN force "was a conflict between strong aggressive impulses seeking an outlet and the inability to express them. This rational conflict, with its intra- and extrapsychic consequences, turned out to be the most important emotional problem for the UN soldiers."

This same observation well may hold when considering the underlying causal cognitive dynamics of many of the different types of PTSD victim studied in the Center. The range of these groups, which includes political hostages, victims of bank robberies, casualties of North Sea oil-rig disasters, plane and helicopter crashes, etc., gives some confidence in the generalizability of Weisaeth's findings. But there is more to it than this. While the range of victims studied is outstanding--covering military and civilian samples, and victims of accidental as well as premeditated catastrophes--the Center's stress on longitudinal study designs, follow-up, and controlled observation, paired with a sensitivity to the necessity for adequate comparison groups, all add to the value of the research. To me, the work conducted in the Center of Disaster Psychiatry serves as a model of what research in this area can, and should, be. I believe that anyone interested in problems of the type discussed on these pages could profit greatly from interaction with Weisaeth's group, and I hope that this report has served as a useful introduction to a major resource on posttraumatic shock disorder, and the human response to catastrophic events.

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Biological Sciences

MOLECULAR BIOLOGY: EUKARYOTIC CHROMOSOME REPLICATION

by Claire E. Zomzely-Neurath. Dr. Zomzely-Neurath is the Liaison Scientist for Biochemistry, Neurosciences, and Molecular Biology in Europe and the Middle East for the Office of Naval Research's London Branch Office. She is on leave until July 1988 from her position as Director of Research, the Queen's Medical Center, Honolulu, Hawaii, and Professor of Biochemistry, University of Hawaii School of Medicine.

The discussion meeting on "Eukaryotic Chromosome Replication" held in London, UK, on 10 and 11 December 1986 was sponsored by the UK's Royal Society. Although most of the participants were from universities and research institutes in the UK, the US, West Germany, Sweden, Norway, Switzerland, and France were also represented.

The presentations by invited speakers were at the usual level of excellence, typical of meetings sponsored by the Royal Society. Several topics were covered under the general title of the meeting. These included chromosome structure and gene replication, viral models for eukaryotic DNA replication, selective protein turnover, mitochondrial DNA replication, initiation of DNA replication in yeast chromosomes, and the effect of inositol lipids on DNA synthesis. Thus, the objective of this meeting was to present the most recent data on various factors involved in eukaryotic chromosome replication. A summary of the presentations at this meeting is given in this article.

The Structure of Chromatin and Its Wider Implications

This topic was discussed by A. Klug (M.R.C. Laboratory of Molecular Biology, University of Cambridge, UK). It is now evident that the DNA of a nucleosome core particle is wrapped tightly around a histone octamer with approximately 80 base pairs (bp) per superhelical turn. Studies of both naturally occurring and reconstituted systems have shown that DNA sequences very often adopt well-defined locations with respect to the octamer. Recent work in Klug's laboratory has provided a structural explanation for this sequence-dependent positioning in terms of the differential flexibility of different sequences and departures from smooth bending.

Klug stated that the "rules" that are emerging for DNA bendability and, from the results of other workers, on permanently bent DNA, are likely to be useful in considering looping and bending of DNA in other processes, in which the DNA is thought to be wrapped around a protein core. There has been controversy, according to Klug, over the higher-order structure of chromatin. X-ray diffraction patterns have now been obtained from oriented 30-nm-diameter filaments and these are consistent with the solenoid model. Physicochemical studies in Klug's laboratory and other studies are consistent with this model.

Chromosome Structure and Gene Regulation

Data suggesting a structure/function relationship between chromosome organization and gene expression was reported by U.K. Laemmli (Department of Molecular Biology, University of Geneva, Switzerland). Laemmli and his group have been able to map specific DNA fragments at the bases of chromatin loops with the help of a novel extraction procedure with lithium 3, 5-diiodosalicylate. One such scaffold-attached region (SAR) was found in the nontranscribed spaces in each repeat of the histone gene cluster on a 657-bp restriction fragment. Exonuclease III digestion has localized two protein-binding domains on the SAR of the histone cluster. Each covers roughly 200 bp and they are separated by a nuclease-accessible region of about 100 bp. These domains are within sequences closely related to the topoisomerase II cleavage consensus.

Laemmli and his group have studied the scaffold association of three developmentally regulated genes of *Drosophila melanogaster* (fruit fly): alcohol dehydrogenase (Adh), the homeotic gene fushi tarazu (Ftz), and Sgs-4--a gene encoding one of the glue proteins secreted by third instar larvae. These investigators found regions attached to the nuclear

SAR's both 5' and 3' of all three genes, defining small domains ranging from 4.5 to 13 kilobases (kb). In the case of Adh, a gene with two promoters, they found two upstream and two downstream SAR's. Those 5' of the gene co-map with regulatory regions for the adult and the larvae transcripts, respectively. For Sgs-4, the 5 SAR covers 866 bp immediately upstream of the transcript, and encompasses the 200-bp regulatory region defined by two deletion mutants that produce little or no Sgs-4 protein. In Ftz, the 5 SAR is found 4.8 kb upstream of the start of transcription within a 2.5-kb element required for a high level of Ftz expression in the early embryo. Sequence analysis of five SAR's revealed clusters of sequences closely related to the cleavage consensus of topoisomerase II. In addition, they contain multiple copies of two sequence motifs; a specific 10-bp A-rich sequence (AATAAA T_cAAA) and another 10-bp T-rich stretch.

The intimate association of the SAR with the upstream enhancer elements, the presence of clustered sequences highly homologous to the topoisomerase II cleavage consensus, and the localization of topoisomerase II in the scaffold suggest to Laemmli a structure/function relationship between chromosome organization and gene expression.

Genetic and Biochemical Studies with Mammalian DNA Polymers and Holoenzymes

Molecular biological studies using calf thymus DNA polymerase α (pol α) holoenzymes were reported by U. Hübscher (Institute for Pharmacology and Biochemistry, University of Zürich-Irchel, Switzerland). The work was carried out in two directions:

1. Molecular cloning of complementary DNA (cDNA) encoding the catalytic core of pol α
2. Specific initiation of DNA replication on the mammalian SS porcine circovirus (PCV) DNA.

A calf thymus cDNA expression library was constructed in λ gt 11 and probed with polyclonal antibody raised against pol α holoenzyme. The probe identified three classes of recombinant phage clones. The three classes, I, II, and III, contained Eco RI-resolvable cDNA inserts of 0.6, 1.0, and 1.9 kb and expressed inducible β -galactosidase as well as calf fusion proteins of 130, 150, and 180 kilodaltons (kDa). The fusion proteins produced by each class reacted specifically with pol α and β -galactosidase-specific antibodies. In the DNA polymerase activity gel analysis of extracts of Class III, *E. coli* lysogen indicated the

presence of a unique, cDNA-dependent, inducible activity band at the position of the 180-kDa β -galactosidase: calf fusion protein. The 180-kDa activity band was purified and immunoselected with anti- β -galactosidase antibodies and was sensitive to the pol α -specific inhibitors aphidicolin, BuPdGTP, and BuAdaTp as well as to monoclonal and polyclonal DNA polymerase α antibodies. The results indicated that the cDNA carried by class III phage recombinants encoded the catalytic site of pol α .

The ss DNA genome of PCV is a covalently closed circle. Hübscher and his group used this template to study *in vitro* initiation of DNA replication. Pol α holoenzyme contains polypeptides of 198, 138, 125, 118, 99, 87, 63, 54, 49, and 47 kDa. This holoenzyme is added to prime the ss PCV DNA at one preferred site in the genome. This site has the potential to form secondary structures and a consensus sequence for binding of nuclear factor 1. The pol α holoenzyme includes a polypeptide of 47 kDa (the same molecular mass as nuclear factor 1) and can bind specifically to a nuclear factor 1 consensus sequence. Thus, this *in vitro* system for initiation of DNA replication can be used to dissect the mammalian DNA replication apparatus.

Viral Models for Eukaryotic DNA Replication

One approach to the analysis of eukaryotic DNA replication is to develop cell-free systems that are capable of replicating the simple chromosomes of the animal viruses, such as adenovirus and SV40. This approach has been used by T.J. Kelly, Jr., (Department of Molecular Biology and Genetics, Johns Hopkins University School of Medicine, Baltimore, Maryland). He reported on his studies which were designed to define the nucleotide sequence elements that determine the specificity of initiation of viral DNA replication, and to identify the viral and cellular proteins required for DNA replication. Data obtained by Kelly and his group from analysis of mutant templates demonstrated that the origins of replication of both adenovirus and SV40 consist of several functionally distinct sequence domains. Reconstitution experiments *in vitro* resulted in the identification and characterization of a number of viral and cellular proteins that are required for initiation and chain elongation.

In recent studies, Kelly and his group have purified three cellular proteins that recognize specific sequence elements within the adenovirus origin of replication. They have also defined the roles of mammalian topoisomerases I and

II during the chain elongation and segregation steps of DNA replication in SV40.

Studies on the replication of DNA containing the polyoma (Py) origin of replication, and of DNA containing the SV40 origin of replication were described by R. Wobbe (Department of Molecular Biology and Virology, Memorial Sloan-Kettering Cancer Center, New York City). R. Wobbe, a member of J. Hurwitz's group, replaced Hurwitz, who was unable to be present at the meeting. These investigators found that each system specifically requires its homologous large T-antigen and its origin for replication. They have shown that both reactions require the DNA polymerase:DNA primase complex for replication. The host cell source of this complex plays an important role in discriminating between replication dependent on SV40 T-antigen and replication dependent on Py T-antigen. Polymerase:primase complex from He La cells supports SV40 T-antigen-dependent replications but is virtually inactive with the Py system. In contrast, polymerase:primase complex from mouse cells supports Py T-antigen-dependent replication but does not support SV40 replication. These investigators have reconstructed the replication of the SV40 DNA system with partially purified enzymes. Evidence has been obtained that the Py T-antigen and SV40 T-antigen are multifunctional proteins that contain binding activities, ATPase and DNA helicase.

T-Antigen and p53 in Viral and Cellular DNA Synthesis

Biochemical and molecular biological studies of the roles of SV40 large T-antigen and the p53 protein were presented by D.P. Lane (Imperial Cancer Research Fund Laboratories, Potters Bar, Hertfordshire, UK). The SV40 large T-antigen was purified by Lane and his group using immunoaffinity chromatography. They found that the isolated protein will initiate DNA synthesis in an *in vitro* system containing a crude cell extract of human cells and plasmid DNA that contains the SV40 viral origin sequences. The purified protein has an ATP-dependent DNA helicase activity. This observation implies that it may be required at the replication fork for the elongation reaction as well as for the initiation reaction.

In infected and transformed cells, large T-antigen is associated with the host-coded p53 protein. Using a range of expression constructs, fragments of the large T-antigen and p53 protein were overproduced in and purified from *E. coli*. The sequence-specific DNA binding activity of large T-antigen was found to be retained by the amino-terminal third of the molecule synthesized in *E. coli*.

The remaining two-thirds of the molecule is able to bind p53 that has been synthesized in either prokaryotic or eukaryotic cells. The activity of these gene fragments in promoting viral and cellular DNA synthesis is currently being studied by Lane and his group.

The N-end Rule of Selective Protein Turnover

Studies on the role of the N-terminus of proteins in selective protein turnover was discussed by A. Varshavsky (Department of Biology, Massachusetts Institute of Technology, Boston). The function of selective protein turnover appears to be for the purpose of discriminating between damaged and undamaged protein. The studies of Varshavsky and his group were designed to ascertain how the cells recognize which protein should be degraded.

When a chimeric gene encoding a ubiquitin: β -galactosidase fusion protein is expressed in the yeast *S. cerevisiae*, ubiquitin is efficiently cleaved off the nascent fusion protein, yielding a deubiquitinated β -galactosidase (β gal). With one exception, this cleavage takes place irrespective of the nature of the amino acid residue of β gal at the ubiquitin- β gal junction. In effect, this result allowed Varshavsky and his group to expose different residues at the N-termini of the otherwise identical β gal proteins produced *in vivo*. The β gal proteins thus designed exhibit a striking diversity of *in vivo* half-lives, from more than 10 hours to less than 3 minutes, depending on the nature of the amino acid exposed at the N-terminus of β gal.

Varshavsky and his group also showed that the N-terminal location of an amino acid is essential for its effect on β gal half-life. The set of individual amino acids can thus be ordered with respect to the half-lives that they confer on β gal when present at its N-terminus (the "N-end rule"). The known N-terminal residues in long-lived intracellular proteins from both prokaryotes and eukaryotes are exclusively of the stabilizing class as predicted by the N-end rule. In contrast, a majority of the N-terminal residues in compartmentalized (e.g., secreted) proteins are of the destabilizing class. The N-end may also account for the function of the previously described post-translational addition of single amino acids to protein N-termini. Thus, the recognition of an N-terminal residue in a protein may mediate both the metabolic stability of the protein and the potential for regulation of its stability.

Chromosome Replication In Vitro

Studies of chromosome replication using a cell-free system derived from unfertilized eggs of *Xenopus laevis* (frog) were presented by R.A. Laskey (Cancer Research Program, Embryology Group, Department of Zoology, University of Cambridge, UK). Laskey and his group developed a cell-free system which initiates and completes semiconservative DNA replication *in vitro*. When demembranated nuclei from *Xenopus* sperm are used as the template, essentially all of the DNA was found to replicate once. Replication of purified DNA was also observed. When purified DNA is added to the system, it becomes assembled into nuclei with double nuclear membranes and nuclear pores. When nuclei are centrifuged into a fresh aliquot of extract, reinitiation of replication is observed. Fractionation of egg extracts of *Xenopus* has led to the identification of proteins involved in chromatin assembly. Laskey and his group are now carrying out studies to identify the components required for nuclear reformation and DNA replication.

Cell-free Replication of Simian Virus 40 (SV40) DNA

Studies of the characteristics of the replication of SV40 DNA in an *in vitro* system as a model for some aspects of eukaryotic chromosome replication were described by B. Stillman (Cold Spring Harbor Laboratory, Cold Spring Harbor, New York). In the presence of SV40 large T-antigen, a soluble extract derived from the cytosol of human 293 cells is capable of efficient replication of plasmid DNA's that contain the SV40 DNA replication origin (ori). Multiple rounds of DNA synthesis occur in this system and yield covalently closed, but relaxed, progeny molecules. Studies on the kinetics of DNA replication have revealed a lag of 10 to 15 minutes before the elongation phase of replication. The lag can be eliminated by preincubation of the template DNA with T-antigen and cellular proteins. During this reaction, which Stillman calls the presynthesis step, a complex of proteins is formed, at ori, which can be isolated and used as a template for immediate DNA replication. Stillman and his group have fractionated the cytosol extract into multiple components, one of which has been purified to homogeneity. If an extract derived from the nuclei of 293 cells is added to the cytosol replication extract, the replicated DNA is preferentially assembled into a chromosome structure. Chromosome assembly is dependent on DNA replication and is modulated by levels of SV40 T-antigen. In contrast to replication in the absence of nuclear extract, multiple rounds of DNA replication

were not observed when the replicated DNA is assembled into chromatin. The nuclear extract appears to contain components that impair the rate of presynthesis complex formation.

Inositol Lipids and DNA Synthesis

Studies of the role of inositol lipids on cell proliferation and DNA synthesis were presented by M.J. Berridge (Agriculture and Food Research Council, Department of Zoology, University of Cambridge, UK). Cell proliferation is controlled by growth factors, some of which act by stimulating a specific phosphoinositide to generate diacylglycerol (DG) and inositol 1,4,5-triphosphate (ITP). A necessary prerequisite for the initiation of DNA synthesis is alkalinization of the cytoplasm. This process is controlled by DG activation of protein kinase C. Another important mitogenic signal appears to be an increase in the intracellular level of calcium, much of which is released from internal stores by the action of ITP. The two major ionic events associated with the onset of DNA synthesis are thus under separate control of the two second messengers derived from the hydrolysis of a membrane inositol lipid. Berridge thinks that interest in this receptor mechanism is likely to grow; recent studies suggest that growth factor receptors are coupled to the enzyme that cleaves inositol lipid by means of a unique G-protein, which may be similar if not identical to the product of the *ras* oncogene.

Mitochondrial DNA Replication

Mammalian mitochondrial DNAs replicate unidirectionally from two distinct strand-specific origins. A round of replication begins at the heavy-strand origin (the "D-loop") where transcripts from an upstream promoter serve as the primers for DNA synthesis. The transition from RNA to DNA synthesis occurs within short, conserved nucleotide sequence blocks and is mediated by specific endonucleolytic cleavage of the primary transcript.

Studies designed to investigate nuclear gene products that function in mammalian mitochondrial DNA replication were described by D.A. Clayton (Department of Pathology, Stanford University Medical School, Stanford, California). An enzymatic component involved in the generation of primer RNA in mouse mitochondria has been identified. It is a sequence-specific endoribonuclease that cleaves single-stranded RNA substrates precisely at one of the transition sites. The other origin, that for light-strand synthesis, is located well apart on the genome and functions only when in a single-stranded template form. This origin

has a defined secondary structure that is the most highly conserved sequence element in mammalian mitochondrial DNAs. Initiation of replication at this origin is by the action of a mitochondrial DNA primase, which is capable of synthesizing a short stretch of ribonucleotides before switching to DNA synthesis. Mitochondrial DNA primase appears to have an associated RNA species and the evidence to date suggests that components of both the D-loop endoribonuclease and the DNA primase are nuclear gene products.

Cell Cycle Control of Fission Yeast

The genes controlling the cell cycle of fission yeast were discussed by P.M. Nurse (Imperial Cancer Research Fund Laboratories, London, UK). There are two major controls during the cell cycle of fission yeast. One acts at the start in late G1 phase and is the point at which the cell becomes committed to the mitotic cycle and initiates the sequence of events leading to S-phase. The second acts in late G2 and determines when mitosis takes place. The gene, *cdc2*, encoding a phosphorylated 34-kDa protein with protein kinase activity, functions at both control points. The protein becomes dephosphorylated and loses its kinase activity in cells arrested at the start. Two genes, *wee1* and *cdc2*, act as negative and positive regulators over *cdc2* activity at the second mitotic point. The *wee1* gene product has homology with protein kinases; this result suggests that phosphorylation has a role in this regulation. Sequencing of various *cdc2* mutants has identified a region of the *cdc2* protein which may interact with these regulators. A further gene, *suc1*, has been identified; its gene product probably binds directly with the *cdc2* protein, and has a role in its own right in the cell cycle.

DNA Replication in Yeast Chromosomes

A study of the initiation of DNA replication in yeast chromosomes was presented by S.E. Kearsey (Cancer Research Campaign, Department of Zoology, University of Oxford, UK). Introduction of defined DNA molecules into cells of the yeast *Saccharomyces* by transformation methods has made it possible to define *cis*-acting DNA sequences which are needed for chromosome replication and segregation. These sequences include autonomously replicating sequences (ARS) which are required for the replication of DNA molecules in yeast cells and are generally thought to correspond to origins of replication. By using methods that assay the mitotic stability of artificial chromosomes, it has been possible to define the nucleotide sequence requirements for

autonomous replication and to identify genes whose products may be involved in DNA replication.

DNA Replication Process in Prokaryotic Systems

A review of the general features of DNA replication in prokaryotes which may have some relevance to eukaryotes was presented by B.M. Alberts (Department of Biochemistry and Biophysics, University of California, San Francisco). Alberts also included studies from his laboratory.

The three different prokaryotic replication systems that have been most extensively studied use the same basic components for moving a DNA replication fork, even though the individual proteins are different and lack extensive amino acid sequence homology. In the T4 bacteriophage system, the components of the DNA replication complex can be grouped into functional classes as follows: DNA polymerase (gene 43 protein), helix-stabilizing protein (gene 32 protein), polymerase accessory proteins (gene 44/62 and 45 proteins), and primosome proteins (gene 41 DNA helicase and gene 61 RNA primase). DNA synthesis in the *in vitro* system starts by covalent addition into the 3' hydroxyl end at a random nick or a double-stranded DNA template and proceeds to generate a replication fork that moves at about the *in vivo* rate and with approximately the *in vivo* base-pairing fidelity. DNA is synthesized at the fork in a continuous fashion on the leading strand and in a discontinuous fashion on the lagging strand (generating short Okazaki fragments with 5'-linked pppApCpXpYpZ pentaribonucleotide primers). Kinetic studies revealed that the DNA polymerase molecule on the lagging strand-rays associated with the fork as it moves. Therefore, the DNA template on the lagging strand must be folded so that the stop site for the synthesis of one Okazaki fragment is adjacent to the start site for the next such fragment, allowing the polymerase and other replication proteins on the lagging strand to recycle.

Conclusion

The Royal Society-sponsored meeting on eukaryotic chromosome replication included studies of replication in *Drosophila melanogaster*, yeast, and *Xenopus laevis*, as well as viral models for DNA replication. Studies of nucleic gene products that function in DNA replication were also presented as well as the role of inositol lipids in DNA synthesis. Research on eukaryotic chromosome replication is less advanced than bacterial chromosome replication. The most recent research on eukaryotic chromosome repli-

cation was presented at this conference, and the information presented shows that many advances in our knowledge of this area have been made recently. Such information is very important in understanding mammalian gene regulation. The invited speakers were from UK, West Germany, and US Laboratories. The presentation and material covered was excellent.

2/19/87

MOLECULAR BIOLOGY: CONFERENCE ON GENETIC ENGINEERING TECHNIQUES

by Claire E. Zomzely-Neurath.

Introduction

The second European seminar on genetic engineering techniques, sponsored by IBC Technical Services Ltd. was held at the Portman Hotel, London, from 20 through 21 November 1986. The scientific program was arranged in the following sessions:

- Isolation of large segments of chromosomal DNA
- Cloning and expression in *E. coli*
- Expression in mammalian cell culture and transgenic mice
- Engineering specific genes.

There were 60 participants from seven different European countries as well as the UK and US. The attendees were about evenly divided between those from the academic and industrial sections. The stimulating and intensive sessions covered a range of topics within each session. A summary of selected presentations is presented in the following section. A detailed account is available in ONRL report 7-009-C.

Isolating Large Segments of Chromosomal DNA Choice and Use of Cosmid Vectors

Cosmid vectors are potentially the most useful DNA cloning vehicles because of their large capacity, but their utility has been severely reduced because of problems of instability and irreproducibility of growth. New vectors that overcome many of these technical problems were presented by P. Little (Chester Beatty Laboratories, London, UK).

The application of recombinant DNA techniques to the study of human genetics has had a revolutionary effect upon our understanding of levels of genetic dysfunction. Where the affected gene can be identified, detailed analysis of DNA

sequence has been possible, identifying specific mutations and allowing a clearer understanding of the nature of the diseased state. However, a major effort of human genetics is now devoted to the isolation of genes that are of unknown functions but that must be responsible for some very common and serious genetic diseases. Huntington's Chorea, Cystic Fibrosis and Duchenne Muscular Dystrophy represent this class of gene. The use of restriction fragment length polymorphisms (RFLP's), of cytologically and molecularly defined deletions and of analysis of large DNA fragments (up to 10^6 base pairs) by pulse-field gel electrophoresis have proved critical in delineating regions of DNA that must contain the affected gene (S). A map of clones of DNA that correspond to such a large amount of DNA can also be used to study, for example, the relationship of DNA sequence to chromosome structure and the higher order structures of DNA sequence. The main problem in cloning a large region of human DNA is the isolation of the high molecular weight DNA.

The new generation of cosmid vectors has made some contribution to the ultimate goal of cloning all of a large region of DNA. Little and his research group have found that no single vector is ideal for this and have proposed that the best results are obtained with the three different vector systems: high copy number *lambda ori* cosmids, low copy number (but inducible) cosmids, and phage *lambda* vectors. Two out of three of these systems are now available and according to Little, mapping information will provide the necessary basis for a detailed, statistically significant description of clone distribution and coverage.

Techniques for Chromosome Walking.

Vector and cloning techniques have been developed to allow the molecular analysis of genetic distances in mammals, an essential step in the identification of genes defined by mammalian mutations. Cloning techniques to simplify chromosome walking, to clone the ends of large fragments, to clone sequences containing rare restriction fragment sites as well as approaches to identify overlapping cosmids were described by H. Lehrach (European Molecular Biology Laboratory, Heidelberg, West Germany).

The size separation of standard DNA gel electrophoresis systems is limited because large DNA molecules migrate independent of their molecular weight. This effect can be overcome by the use of pulse-field gradient gel electrophoresis or field inversion gel electrophoresis in combination with restriction enzymes which cleave only limited areas of mammalian DNA. Systems of this type allow

the demonstration of physical linkage of genetically closely linked DNA fragments and, using either information from single and double digest patterns or partial restriction mapping procedures, restriction maps covering regions of millions of base pairs can be carried out. Using these techniques Lehrach and his coworkers have analyzed DNA sequences of human and mouse mutations--for example, the DNA sequences around the Duchenne Muscular Dystrophy locus and DNA sequences in the vicinity of Huntington's Chorea and Cystic Fibrosis mutations.

Another approach used by Lehrach and his group is that of jumping libraries. Chromosome walking--i.e., the repeated use of fragments from the end of a previously isolated clone to isolate clones extending further than the initially isolated DNA clone (that is, to have overlapping sequences)--has been used successfully in walking across genetic distances in organisms like *Drosophila melanogaster* (fruit fly). But this technique is much less successful in mammalian DNA because of its very large size. To allow steps larger than the limited capacity of the available cloning vectors, the construction of chromosome jumping libraries is based on the deletion of all but the ends of large DNA fragments by a series of manipulations carried out before the cloning step. Lehrach and his group have especially concentrated on chromosome jumping libraries from DNA digested to completion with restriction enzymes which clone only limited areas of mammalian DNA. This reduces the complexity of the libraries to be constructed and screened and simplifies the analysis of the resulting clones. These investigators have constructed human jumping libraries as well as libraries from mouse DNA.

Sequences containing rare restriction sites can be selectively cloned out in the construction of "linking clone libraries" and constitute a well-defined subset of the entire genome. One application is the use of such sequences to link up pairs of jumping clones. Alternatively, or in addition, DNA fingerprinting techniques can be used to identify adjacent linking clones by their shared jumping clones. Lehrach and his group are testing some of these possibilities using linking clones from the area of the Huntington's Chorea gene.

An alternative strategy to isolate clones from an area around an available marker clone or to clone sequences adjacent to rare cutting sites within such an area is the cloning of DNA fragments from pulse-field gradient gel electrophoresis (PFG) size fractionation. In general, gel electrophoresis only provides enrichment of 10- to at most 100-fold. Therefore,

Lehrach has provided a second enrichment by using somatic cell hybrids in which, for example, single human chromosomes or chromosome subregions have been transferred into a hamster or mouse cell line, allowing the differentiation of human and hamster or mouse clones by hybridization with total human DNA or cloned human repetitive DNA sequences. Lehrach has started experiments to generate clones in the Duchenne Muscular Dystrophy regions as well as the regions of the Huntington's Chorea and Cystic Fibrosis loci.

Lehrach and his group are also developing strategies to generate ordered clone libraries which do not require, or at least minimize, the individual manipulation of clones for the purpose of providing a high-resolution map of human chromosomes in order to extend the genetic map down to a resolution of kilobase pairs for the ultimate analysis of regions of the genome by DNA sequencing. In this approach, the identification of overlapping clones relies on shared hybridization (or nonhybridization) to a fairly large number of oligonucleotide probes selected to randomize with approximately one in three cosmids. Shared hybridization to single probes gives very little information while very similar hybridization of many probes will constitute an overwhelming case for detection of an overlap (analogous to detection of linkage). Lehrach considers this approach to be attractive since one can carry out the hybridization experiments on any number of DNA's from cosmid or lambda clones, distributed as a regular array on membrane filters. Preliminary studies carried out by Lehrach and his group have shown promising results.

Exploiting *E. coli*

The Synthesis of Fusion Proteins in *E. coli* and Their Use in Raising Antibodies: From Gene to Antigen. The application of modern cloning and sequencing techniques often results in the identification of a new potential protein encoding genes on the basis of detection of long open reading frames (ORF) within the DNA sequence. The task is then to efficiently detect and determine the nature of the product of the ORF. D.P. Lane (Imperial Cancer Research Fund, Clare Hall Laboratories, UK) described the use of fusion protein expression vectors to raise antibodies against ORF's and the analysis of their biochemical and biological properties. Lane presented one example of this approach, namely, analysis of the SV40 large T ORF using the pUR, pUC and pSEM Cat_{R1} vectors. Lane and his group have made extensive use of the pUR series of vectors and have constructed and analyzed numerous viral and cellular

genes such as yeast genes, polypeptide hormone precursor genes, papovavirus gene, oncogenes, and the Large T gene described in his presentation.

In summary, ORF expression vectors permit the isolation of monoclonal and polyclonal antibodies to defined domains of protein antigens and can also be used in direct functional studies. The enhanced immunogenicity of fusion proteins can be exploited to isolate antibodies of novel specificity. The same fusion protein constructions also allow accurate epitope mapping of existing antiprotein antibodies.

The Purification of Foreign Polypeptides Expressed in *E. coli*. Gene cloning and expression in *E. coli* can provide an abundant source of foreign (eukaryotic) polypeptides whose use is limited by low, natural availability. The polypeptides can be located in the cytoplasm of *E. coli* or secreted through the cell membrane. However, the mode of expression affects both the efficiency of production and the nature of the polypeptides themselves. This has implications for the purification techniques which must be developed, as discussed by F. Marston (Celltech Ltd., Slough, UK).

Recombinant products from *E. coli* accumulate to greater levels when expressed intracellularly (up to 25 percent of total cell protein) than when they are secreted (up to 1 percent of total cell protein). However, many heterologous polypeptides located in the cytoplasm are insoluble and require specific solubilization techniques to yield active products for purification. Insoluble recombinant proteins accumulate in *E. coli* in the discrete form of inclusion bodies. This is useful for purification as they are dense and readily sedimented during low-speed centrifugation. Further purification can be achieved by washing the isolated inclusion bodies with detergent or urea. To recover active soluble protein, the isolated inclusion bodies must be denatured and unfolded (conditions must then be adjusted to allow the polypeptides to refold into the correct conformation).

Small polypeptides, when expressed directly in *E. coli*, are often degraded rapidly. This can be prevented by expressing the eukaryotic genes as fusions with partial or entire bacterial coding sequences. There are many examples of fusion proteins which are in an insoluble form when synthesized in *E. coli* such as somatostatin, human calcitonin, β -endorphin, bovine growth hormone, urogastrone, etc. The fusion proteins contained in inclusion bodies must be solubilized before further purification is possible, and this has been achieved by the use of

detergents and denaturants. These solubilization agents were maintained in the buffers used for column chromatography purification. Purified fusion proteins have been used in diagnostic development and analytical research but, in general, the foreign polypeptide is required to be free from the bacterial sequence. The strategy used to achieve this is to place a cleavage site between the C-terminus of the prokaryotic sequence and the N-terminus of the eukaryotic coding sequence. A unique cleavage site, not present in the sequence of the recombinant protein, is the ideal arrangement, so that the foreign protein itself is not cleaved. Cleavage can be carried out by either chemical or enzymatic approaches. Solubilization may be required before the cleavage reaction can be performed. When enzymatic cleavage is used, conditions for solubilization are required in which the enzyme is still active.

Fusion proteins can be constructed to facilitate purification by using bacterial or synthetic nucleic acid sequences coding for peptides which can be isolated by affinity chromatography. One approach was to fuse a sequence coding for polyarginine at the 3' end of the epidermal growth factor (urogastrone) gene. Cation exchange chromatography, used to purify the fusion protein, was particularly effective, since most bacterial proteins are acidic and therefore negatively charged at the pH of 5.5 which was used. Carboxypeptidase B was used to digest the polyarginine tail, and further cation exchange chromatography yielded highly purified hormone.

After solubilization from inclusion bodies and cleavage for fusion proteins, the polypeptides must be refolded to yield active protein. Refolding is achieved by buffer exchange out of denaturing conditions using, for example, dialysis or dilution. Small polypeptide hormones such as β -endorphin and calcitonin apparently fold spontaneously. For larger polypeptides, specific conditions must be defined in order to obtain correctly folded protein. According to Marston, a key factor influencing the recovery of active product, is protein concentration: this must be low enough to allow intramolecular interactions to occur in preference to intermolecular interactions. Marson presented refolding protocols for several cloned eukaryotic proteins such as insulin, β -globin and pro-chymosin.

There are advantages and disadvantages in using *E. coli* to express heterologous proteins. Large amounts of foreign proteins can be synthesized per liter of fermentation mixture by intracellular expression but the products are

often insoluble. Secretion from *E. coli* overcomes the insolubility problem but expressed yields are low. If *E. coli* is to be used as a secretion system, then further development is required. Eukaryotic polypeptides synthesized by and purified from *E. coli* are now in therapeutic use: interleukin-2, interferon- α , interferon- β , interferon γ , and tissue necrosis factor (TNF) are currently in clinical use. Thus, it must be concluded that *E. coli* is a valid production system for the manufacture of therapeutic proteins.

Expression in Mammalian Cell Culture

Eukaryotic Expression Vectors. Genetic engineering provides the potential to produce in large quantity scarce or even completely novel proteins. However, it has become clear that prokaryotic expression (*E. coli*) systems are often inappropriate for complex eukaryotic proteins. The fermentation of animal cells, transformed with suitable eukaryotic vectors, can provide a viable alternative, as discussed by C. Hentschel (Celltech Ltd.).

The evolution of eukaryotic expression vectors has relied on progress in the methodology of gene transfer in mammalian cells. There are several methods for directly transferring DNA to the nuclei of mammalian cells. A commonly used procedure exploits the fact that DNA, for example, cloned in a bacterial vector, can be taken up by cells either as a coprecipitate with calcium phosphate or bound to DEAE-dextran. Once inside the nucleus, the DNA can become inserted, essentially at random, into one or more of the host chromosomes. Stable cell lines containing integrated DNA are generated at low frequencies, so a selectable marker is usually included on the vector to eliminate nontransformed cells. An important and highly efficient alternative form of gene transfer can be provided by viral infection--for example, by retroviral vectors.

Introduction of genomic DNA sequences into mammalian cells by one of the above techniques can be sufficient to lead to detectable expression of transferred genes provided that essential control sequences are present in addition to the coding region. One way to provide the signals specifying high-level expression is to insert the coding sequence into the genome of an animal virus at an appropriate location downstream of a strong promoter in place of one or more viral genes. Adenovirus vectors based on this approach have been used to express a number of genes efficiently. Retroviruses have similarly been used to express high levels of commercially useful proteins. An alternative form of vector

construction combines functional elements obtained from different sources. In this case, a complete transcription unit is formed by providing the cloning sequence firstly with a suitable promoter-enhancer combination for efficient transcription in the particular cell type chosen. Secondly, appropriate transcribed sequences 5' and 3' to the protein-coding may be provided to enhance translation and message stability. It may also be advantageous to coexpress a transacting transcriptional activator gene in the same cell.

The amount of protein product of transfected genes is often found to be roughly proportional to the number of functional copies of the gene present. Thus, a strategy which allows an increase in the copy number of the integrated genes is clearly desirable. This can be done by gene amplification. If cultured cells are subjected to sequentially increasing amounts of toxic drug, variant clones can frequently be selected which are more resistant to the drug than wild-type cells. In the majority of cases, this is due to the overproduction of an essential enzyme whose activity the drug is inhibiting. The overproduction of the enzyme has frequently been shown to be due to an increase in the copy number (i.e., amplification) of the structural gene coding for the enzyme. Coamplification of an unrelated structural gene with a dihydrofolate reductase (DHFR) gene has been used to produce several commercially useful proteins in large amounts, and the highest reported levels of expression have been achieved with this system. Some examples are hepatitis B surface antigen, tissue plasminogen activator (tPA) and interferon- β .

An alternative method of achieving persistence of the introduced gene in the host cell is to provide an origin of DNA replication as part of the vector. A particularly useful animal virus for the construction of expression vectors has been the bovine papillomavirus (BPV) which replicates episomally in rodent fibroblast cells. The relatively high copy number obtained has led to high levels of expression for a number of genes in mouse fibroblasts.

Conclusion

The development of techniques for cloning segments of DNA has made a major impact on biology. As a result, there has been remarkable progress in our understanding of gene organization and expression with continuing development of genetic engineering. The impact of this technology has not only been felt in academic circles but also in industry where the potential of having a microorganism

synthesize gene products of industrial and pharmacological importance was quickly realized. The presentations at this meeting have shown how gene cloning technology has continued to develop. Thus, it is now possible to introduce cloned genes into whole animals and plants. The advantages and disadvantages of expressing cloned genes in bacteria, yeast, and cultured mammalian cells were presented at this conference with the major contributions from the UK and West German laboratories.

1/20/87

BIOELECTROCHEMICAL SYMPOSIUM: FORMATIONS AND REACTIONS OF PEROXIDES IN BIOLOGICAL SYSTEMS

by Claire E. Zomzely-Neurath.

This conference was held from 22 through 24 October 1986 at the Bischenberg Conference Center, Obernai (Strasbourg) France. The Bioelectrochemical Society organized this specialized symposium under the auspices of the Commission of Science and Technology of the Council of Europe to provide a critical review of recent studies on the topic of the formation of peroxides and free radicals from oxygen. The basis for this focused conference was the evidence of studies indicating the importance of peroxides formation in biochemistry, physiopathology, and pharmacology. The interdisciplinary aspect of the research developed in this area was emphasized by bringing together chemists and biophysicists as well as researchers in the medical sciences. There were 60 participants from eleven different countries including the US, Canada, Israel, and Japan with the largest number from the UK and Europe. The symposium included oral presentations by invited speakers as well as selected original contributions and poster sessions.

The meeting covered the following topics:

- Physical chemistry of peroxides and oxygen-free radicals
- Radiolytical, electrochemical, chemical, and photochemical formation of peroxides and oxygen-free radicals in living systems and model systems
- Analytical methodology
- Biochemical alterations and protective mechanisms induced by peroxides and oxygen-free radicals in living systems

- Scavengers of oxygen-free radicals and peroxides as protective drugs.

The proceedings of the conference will be published in a special issue of the journal *Bioelectrochemistry and Bioenergetics* in about 4 months.

A summary of some of the relevant and interesting topics discussed at this specialized conference, which received support from the Office of Naval Research, London, is presented in the following sections.

Thermodynamics of Reactions Involving Oxyradicals and Hydrogen Peroxide

Energetics of reactions involving hydrogen peroxide and oxyradicals were reviewed by W.H. Koppenol (Department of Chemistry, University of Maryland, Catonsville). Briefly, thermodynamic data for radical species such as $\cdot\text{OH}$, $\text{O}_2^{\cdot-}$, and $\text{O}_3^{\cdot-}$ are now available. Such data allow one to calculate Gibbs energy changes of reactions of metal complexes, metalloproteins, organic molecules, and halogen-containing species in which these radicals participate. Gibbs energy changes are also computed with the help of reduction potentials. If a particular potential is unknown, a thermodynamic cycle is used to regenerate a reasonable estimate.

Role of Metal Complexes in the Formation/ Detoxification of Active Oxygen Species

The role of metal ions and their complexes in DNA damage was discussed by G. Czapski (Department of Physical Chemistry, Hebrew University, Jerusalem, Israel). He showed that copper complexes of 1,10-phenanthroline and some substituted 1,10-phenanthrolines cleave DNA. Generally the damage is attributed to hydroxy radical, which is formed through the Haber-Weiss reaction. In most cases, this reaction occurs between ternary metal complexes with the biological target and hence is defined as a "site specific mechanism." In these systems, $\text{O}_2^{\cdot-}$ drives the cycle through the reduction of copper. On the other hand, some copper complexes catalyze the dismutation of $\text{O}_2^{\cdot-}$ and thus should protect the systems from $\text{O}_2^{\cdot-}$ toxicity. Czapski showed that the toxicity of these complexes can be explained on kinetic grounds. Thus, rate and equilibrium constants can help to determine whether the effects of metal ions on their complexes are protectors of $\text{O}_2^{\cdot-}$ toxicity or act as sensitizers of the toxic effects of $\text{O}_2^{\cdot-}$. For example, copper ions protect DNA from the toxic effects of the antibiotic, bleomycin.

Effect of Bleomycin on the Stability of Radiolytically Produced DNA Peroxides

The possibility that combined cancer treatment procedures using both radio-

therapy and chemotherapy may exhibit synergistic effects has led to extensive biological studies. To understand the basic chemical mechanisms of the synergistic effects of irradiation and redox-active antitumor agents, studies were carried out by D. Beoker-Betts, J. Frew, P. Jones, and G. Scholes (Radiation and Biophysical Chemistry Laboratory, School of Chemistry, University of Newcastle upon Tyne, UK). These researchers investigated the effects of transition metal ions (Fe II, Fe III, Co II, Mn II), chelating agents, and the iron complexes of the antitumor drug bleomycin on the stability of peroxide species generated in the γ -radiolysis of aqueous oxygen-containing solutions of DNA. Their rationale for this approach is that homolytic decomposition of DNA peroxides (hydroperoxides formed from initial attack by $\cdot\text{OH}$ radicals on the pyrimidine moieties) may lead to further degradation of the polynucleotides which, at the biological level, could enhance radiation sensitivity. Spectrophotometric techniques for the determination of peroxides were optimized to allow detection and measurement of small amounts (1×10^{-6} to 1×10^{-4} mol/mL) of hydrogen peroxide and of organic peroxides (pyrimidine hydroperoxides) in the presence of radiolysis products and unmodified material. Of the transition metals used, only Fe(II) had any significant effect on the stability of peroxidic material. Where peroxide decay in DNA occurred, chelating agents were found to arrest the trend. Bleomycin, which is able to chelate both Fe(II) and Fe(III) ions, exhibits a synergistic decay of organic peroxides formed in DNA when chelated to Fe(III) ions.

Electrochemical or Chemical Reduction of Oxygen dissolved in Aqueous Solutions

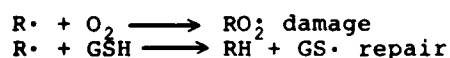
Physicochemical studies of electrochemical and chemical reduction of dissolved oxygen in aqueous solutions were presented by R. Buvet (Laboratory of Bioelectrochemical Energetics and Biochemistry, University of Paris Val de Marne, Créteil (Paris), France). Buvet reviewed experimental data, as well as theoretical reasons, showing that the oxygen dissolved in aqueous solutions cannot be reduced to water by a 4-electrons/4-protons process occurring at its equilibrium redox potential. This kinetic blocking apparently also takes place in biochemical enzymic reductions.

The electrochemical reduction of oxygen occurs on noncatalytic gold electrodes above pH 12 through a quasi-reversible 2-electrons/1-proton process producing HO_2^- . Between pH 5 and 12, the reduction on gold electrodes takes place at +0.15 V/NHE and globally produces H_2O_2 .

through a mechanism which probably involves successive steps of production and dismutation of $O_2^{\cdot -}$. Chemically, the noncatalytic reduction of O_2 by reversible reduction never occurs rapidly when the reducing agents have redox potentials higher than 0.2 V/NHE. A typical 2-electrons/2-protons rapid reducer is hydroquinone. However, the oxygen reduction takes place only when the pH goes above 8.3 and the redox potential range corresponds roughly to that of 0.2 V/NHE. Hydroquinone also reduces H_2O_2 by inducing the degradation through hydroxylation of the produced quinone. From these data, Buvel concludes that any reversible reducing agent able to deliver electrons at redox potentials lower than about +0.2 V/NHE necessarily induces the rapid formation of hydrogen peroxide in living tissues when it comes into contact with dissolved oxygen.

Peroxy Free Radicals and Radiation Injury

Oxygen has long been known to sensitize cells and animal tissue to the lethal effects of ionizing radiation. Although the exact mechanism of sensitization is still being debated, it is widely accepted that oxygen free radicals are involved in the damaging processes. The role of peroxy radicals in radiation-induced lipid peroxidation and in damage to proteins was discussed by R.L. Willson (Biochemistry Department, Brunel University, UK). Of the various mechanisms proposed, the formation of organic peroxy radicals (RO_2^{\cdot}) on sugar or base residues of nucleic acid, thereby preventing repair of the parent organic radical, has received considerable attention.



The research of Willson and his group as well as that from several other laboratories has indicated the superoxide dismutase (SOD) and other antioxidants exert a protective action in radiation damage due to peroxy free radicals. Recent studies with yeast alcohol dehydrogenase and alpha-1-protease inhibitor, in particular, indicate that SOD but not apo SOD or simple copper complexes may have a role in protecting cells from radiation-induced peroxy radical damage.

Fatty Acid Peroxyl Radicals

The generation and reactivities of fatty acid peroxyl radicals was discussed by W. Bors, M. Erben-Russ, M. Saren (GSF Research Center, Institute for Radiobiology, Neuherberg, West Germany). Peroxyl radicals, derived predominantly from polyunsaturated fatty acids (PUFA) are

obligatory intermediates during lipid peroxidation and autoxidative degradation. Kinetic and product studies in organic solvents and buffers have settled many questions about the primary mechanism of such processes. However, a drawback of these nonenzymatic studies was always the presence of several isomeric radicals.

In an attempt to overcome these difficulties, Bors et al. established a pulse-radiolytic procedure of generating one individual fatty acid peroxyl radical (linoleic acid 13-peroxyl radical) and compared its kinetic properties with an isomeric mixture of linoleic acid peroxyl radicals. Since these species could not be observed directly, their interaction with flavones functioning as radical-scavenging antioxidants in aqueous solution was evaluated. The fact that the bimolecular rate constants for the scavenging of the linoleic acid peroxyl radicals by flavones exceeded those found for α -tocopherol with other peroxyl radicals is consistent with the following:

- Fatty acid peroxyl radicals are highly reactive intermediates
- Certain flavones are very effective radical scavengers
- Their interaction seems to occur most efficiently at the lipid/water interface.

Aldehydes and Lipid Peroxidation in Cellular Membranes

The formation, reactions, and toxicity of aldehydes produced during the course of lipid peroxidation in cellular membranes was reviewed by A. Benedetti (Institute of General Pathology, University of Sienna, Italy). Peroxidation of unsaturated fatty acids gives rise to aldehydes as secondary oxidation products, the primary products being hydroperoxides. A special class of aldehydes, 4-hydroxyalkenals, have been shown to originate in autoxidizing chemical systems and that these aldehydes exhibit a number of important biological effects.

Interest in lipid-derived aldehydes as putative mediators of cellular damage has greatly increased since the demonstration that 4-hydroxyalkenals and, in particular, 4-hydroxynonenal are formed during the course of peroxidation of liver microsomal lipids. Additional studies showed a whole pattern of carbonyls originating from peroxidation of both liver microsomes and isolated hepatocytes.

The reactions of the various classes of aldehydes have been studied extensively by Benedetti and others. As far as 2-alkenals and 4-hydroxyalkenals are concerned, the main reaction, under physiological conditions, is the "Michael

addition" with -SH of low molecular weight thiols, proteins, and enzymes. This reaction is responsible for the inactivation of a number of enzymatic systems. Under certain conditions, 2-alkenals and 4-hydroxyalkenals can also react with amino groups of amino acids. However, the reactivity with amino groups is two to three orders of magnitude lower than with -SH groups.

The effects of 4-hydroxyalkenals (especially 4-hydroxynonenal) in biological systems have been studied extensively, and a large number of inhibiting activities on cellular and subcellular functions have been reported. Recently, it has been shown that 4-hydroxynonenal is a good substrate for both cytosolic GSH transferases and alcohol dehydrogenases. The *in vivo* formation of aldehydes in the liver of animals intoxicated with pro-oxidants has also been shown in two recent lines of research: (1) evidence was found for aldehydes (very likely alkenals) bound to the liver microsomal proteins of rats intoxicated with CCl_4 or BrCCl_3 and (2) 4-hydroxynonenal and a number of aldehydes have been detected in the free form in the liver of mice intoxicated with bromobenzene.

Electroanalytical Approaches to the Determination of Lipid Peroxides

Two complimentary electroanalytical methods have been developed for the determination of lipid peroxides in physiological fluids by M.O. Funk (Department of Chemistry, University of Toledo, Ohio). Both employ electrochemical detection using high-pressure liquid chromatography (HPLC) as the means for enhancing the sensitivity of the measurements. Samples containing organic peroxides including lipid peroxides can be analyzed directly using a modified polarographic detection for reversed phase HPLC determinations. The limit of detection for organic peroxides was 5×10^{-9} M while a value of 25×10^{-9} M for fatty acid hydroperoxides was obtained. Because the technique employs HPLC, the separation and determination of the components of mixtures of peroxide-containing compounds can be readily obtained. Funk carried out the chromatographic and electrochemical characterization of a series of structurally diverse lipid peroxides. In a different approach, the determination of the oxidized glutathione formed during the reduction of lipid peroxides by glutathione peroxidase in an *in vitro* assay was carried out using HPLC with amperometric determination. The sensitivity of the technique was 100×10^{-9} M. The electroanalytical techniques can be readily applied for the determination of peroxide-con-

taining compounds in physiological fluids.

Singlet Oxygen in Biological Systems

Electronically excited molecular oxygen ($^1\text{AgO}_2$) is of increasing interest in biology and medicine. An improved method for determination of $^1\text{AgO}_2$ was reported by H. Wefers and H. Sies (Institute for Physiological Chemistry I, University of Düsseldorf, West Germany). The generation of $^1\text{O}_2$ by photosensitization and in enzymatic model reactions has been demonstrated in a number of cases employing a number of criteria for the identification of $^1\text{O}_2$. However, in more complex biological systems such as cell fractions, $^1\text{AO}_2$ cells and intact tissues, the identification $^1\text{O}_2$ was found to be more difficult. Therefore, Wefers and Sies developed a method for direct measurement of low-level chemiluminescence as it provides a sensitive, noninvasive, and continuous means to detect $^1\text{O}_2$. The transition of $^1\text{AgO}_2$ to the ground state is monitored first with a red-sensitive photomultiplier in the visible spectrum at 634 and 703 nm due to the simultaneous "biomolecular" decay of two molecules of $^1\text{O}_2$, and second, in the near-infrared (1270 nm, "monomol emission")--measurable by a liquid-nitrogen-cooled germanium diode. The effect of D_2O , increasing the lifetime of $^1\text{O}_2$ from about 3 μs to 50 μs , and the effect of $^1\text{O}_2$ quenchers and spectral analyses were taken as evidence for the involvement of $^1\text{O}_2$. Chemiluminescence attributable to $^1\text{O}_2$ emission was studied during hydroperoxide metabolism, and lipid peroxidation and during quinone (menadione and mitomycin C) redox cycling.

The occurrence of $^1\text{O}_2$ in cells generated under physiological conditions or under conditions of oxidative stress may have implications on biological functions at the molecular and cellular levels. Wefers and Sies described reactions of $^1\text{O}_2$ in lipid peroxidation with amino acids (methionine, histidine, and tryptophan, in particular), with the feature of enzyme inactivation. These investigators found that reactions of DNA with $^1\text{O}_2$ led to the damage of guanine. The effect of $^1\text{O}_2$ on the biological activity of intact DNA was studied and showed the loss of transforming activity of plasmid DNA pBR 322 upon exposure to $^1\text{O}_2$ generated by microwave discharge. The D_2O effect and the effects of several quenchers indicated that $^1\text{O}_2$ was the responsible species. Wefers and Sies were also interested in the quantification of $^1\text{O}_2$. Chemical trapping of $^1\text{O}_2$ with the water-soluble 9,10-bis(ethylene)anthracene disulfate, yielding specifically the endoperoxide as oxidation product, was used in the

H₂O₂/NaOCl system and correlated with chemiluminescence in the visible and near-infrared.

Lipid Peroxidation and Endotoxin Shock

Studies on the effects of scavengers on damage by products of free radical lipid peroxidation in shock states was reported by T. Yoshikawa (Department of Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan). The effect of scavengers on shock states was examined in rats. Experimental shock was induced by a single intravenous injection of 100 mg/kg of endotoxin (*E. coli* 055: B5 lipopolysaccharide B, Difco). After the injection of endotoxin, systolic blood pressure was reduced and heart rate was increased. Activities of serum lysosomal enzymes such as acid phosphatase, B-glucuronidase, and cathepsin B were increased. Serum thiobarbituric acid reactive substances, which are important and damaging products of free radical lipid peroxidation, were significantly increased and serum α -tocopherol levels were significantly decreased.

The subcutaneous injection of superoxide dismutase (SOD, 50 mg/kg) at one and 12 hours before the administration of endotoxin prevented the reduction of systolic blood pressure and the increase in serum acid phosphatase, B-glucuronidase, and cathepsin B activities. The subcutaneous injection of catalase (1 mg/kg) at one and 12 hours before the treatment with endotoxin had the same effect as the SOD. These results indicated that oxygen-derived free radicals can affect the experimental shock states and that the free radical scavengers (SOD, catalase) play an important role in the prevention of these pathological conditions.

Lipid Hydroperoxides in Blood Cell Pathology

The effect of lipid hydroperoxides on red cell membranes in sickle cell anemia was discussed by C. Rice-Evans (Department of Biochemistry, Royal Free Hospital and School of Medicine, London, UK). Within the red blood cell there normally exists a balance between the spontaneous oxidation of hemoglobin to the superoxide radical and methemoglobin and the restoration of this oxidized hemoglobin to its normal functional state. In certain blood diseases--for example, sickle cell anemia--the reduction mechanisms of the cell are not able to counteract the spontaneous oxidation efficiently. This conversion leads to the accumulation of iron-containing breakdown products of hemoglobin which may bind to the cellular membrane. Such species have a role in the decomposition of membrane lipid hydroperoxides. Studies by Rice-

Evans and her group showed the presence of lipid hydroperoxides in the sickle cell membrane and the propagation of oxidative damage by iron-catalyzed production of alkoxy and peroxy radicals. These factors cause continued oxidative stress and contribute towards the pathophysiology of the disease.

Effect of Ebselen on Hydroperoxide Metabolism

Studies of the protective effect of a new drug, Ebselen, on the damaging effects of hydroperoxides were presented by G. Tiegs and A. Wendel (Physiological Chemistry Institute, University of Tübingen, West Germany). Ebselen (2-phenyl-1, 2-benzisoselenazol-3 (2H) one) (developed by A. Nattermann and Co., Cologne) is a nontoxic new organic selenium compound which exhibits anti-inflammatory activity in various animal models after oral administration. *In vitro*, the compound catalyzes a glutathione (GSH) peroxidase-like reaction--i.e., the reduction of a variety of hydroperoxides by GSH with similar kinetics as the enzyme. However, the selenium moiety of Ebselen is not incorporated into the selenoenzyme GSH peroxidase.

Recently, Tiegs, and Wendel have found that Ebselen inhibited the rat leukocyte 5-lipoxygenase activity *in vitro*. Thus, Ebselen has a potential for use against pathological conditions associated with the occurrence of activated oxygen species. In the present study, these investigators provided *in vivo* evidence that Ebselen interferes in a dose-dependent manner with the formation of hydroperoxyeicosatetraenoics in mouse liver, which are likely to be involved in a process of leukotriene-mediated hepatotoxicity. Male mice sensitized by 700 mg/kg galactosamine developed fulminant hepatitis when cotreated with 22 μ g/kg of endotoxin. Oral doses of about 1 mg/kg Ebselen significantly protected the animals against this liver damage, as shown by serum enzyme release and histopathological evidence. The model was evaluated by administration of different prostanoid or lipoxygenase inhibitors. GSH depletion also prevented the manifestation of galactosamine/endotoxin-induced hepatitis, indicating the involvement of peptido leukotrienes in this pathogenic process.

Method for Determination of Electrochemically Oxidizable Components in Human Urine

An electrochemical method that can be used for the analytical determination of normal, pathological, and pharmaceutically electroactive catabolites present in urine was presented by M. Moritet and R. Buret (Laboratory of Electrochemical

Energetics and Biochemistry, University of Paris, Val de Marne, Créteil (Paris), France). The method consists of measuring the electrolysis current relating to the (oxidoredox) of those compounds in a capillary graphite paste electrode impregnated with the studied urine and subjected to a linear sweep of electrode potential. The intensity-potential diagrams obtained show series of more or less separated peaks with amplitude proportional to concentrations. The procedure shows immediately, economically, and visually, without preliminary separation, the presence and quantities of urinary electroactive components such as ascorbic and uric acids, xanthurene and oxalic acid, tryptophane catabolites, tyrosine, and many pharmaceutical catabolites at characteristic potentials. Such a rapid, low-cost, polyvalent, and automatizable analytical technique should be very useful for diagnosis of many kinds of diseases and therapeutic follow-up. Its use has been implemented for classifying consulting room patients and for the therapeutic followup of patients with leukemia and subject to total body irradiation.

Effects of Ionizing Radiation on Artificial (Planar) Lipid Membranes

The ion carriers valinomycin and nonactin were investigated as probes for radiation-induced structural changes of lipid membranes by M. Strössle and G. Stark (Faculty of Biology, University of Constance, West Germany) and M. Wilhelm (Radiation Chemistry Division, Hahn-Meitner Institute for Nuclear Research, Berlin, West Germany). Planar lipid membranes in the presence of the ion carriers valinomycin or nonactin were irradiated with 14 MeV electrons from a linear acceleration (Linac). A strong increase of the membrane conductance of up to more than two orders of magnitude was observed. A kinetic analysis of the carrier transport model based on current-voltage curves and on voltage-jump relaxation experiments was performed as a function of radiation dose. Only the translocation rate constant (k_{ms}) of the charged carrier-ion complex was found to be influenced by irradiation. The effect is interpreted as an increase of the polarity (dielectric constant) of the membrane interior induced in the presence of polar products of lipid peroxidation. A combined action of the OH^- and HO_2^- radicals appeared to be responsible for the phenomena. At large radiation doses, a reduction of the membrane conductance was observed. It was interpreted as an increased microviscosity, possibly caused by cross-linking of fatty acid residues. Thus, ion carriers represent sensitive

probes of radiation-induced membrane damage.

Conclusions

The topics presented at this conference emphasized the importance of peroxides formation and reactivity in biological systems. The formation of peroxides and free radicals derived from oxygen can be induced by the action of radiolytical, electrochemical, chemical, and photochemical events with resultant damage to cellular components, including DNA. The prevention of such damage by various compounds such as superoxide dismutase and glutathione was also covered.

2/19/87

BIOTECHNOLOGY: CONFERENCE ON LARGE-SCALE PRODUCTION OF MONOCLONAL ANTIBODIES

by Claire E. Zomzely-Neurath.

A 1-day conference on the large-scale production of monoclonal antibodies (Mabs) sponsored by the Biotechnology Group of the Society of Chemical Industry was held in London, on 9 December 1986 at the society's headquarters. The intensive conference dealt with topics including production of Mabs in airlift reactors, immobilized cell culture systems, antibody production in cell cultures, and factors affecting hybridoma viability. Total attendance was 123, with participants from 12 European countries including the UK and a few from Canada. Because the topic of the conference was the scale-up of the production of Mabs, 64 percent of the participants represented industrial organizations; the remainder came from academic institutions.

Over the past few years, commercial interest in Mabs has increased rapidly, especially in the areas of diagnosis, tumor imaging, cancer therapy, and immunopurification. A predicted market value of Mabs has been estimated at \$2.7 billion by 1990. Some applications require only milligram quantities of Mabs whereas others, such as cancer therapy, use much greater quantities: doses may be in grams per patient per year. The technology for producing Mabs in a laboratory scale consists of injection of hybridoma cells intraperitoneally in mice where they proliferate and secrete Mabs into the ascites fluid which is then collected for the purification of Mabs. However, there are logistical limitations on scale-up (100 to 150 mice would be required to produce one litre). Therefore, the method

of the culture of hybridoma cells in nutrient media *in vitro* is the technique being used for large-scale production of Mabs. The antibodies are secreted into the surrounding medium, producing one of two types of starting material. From stirred or airlift fermenters, the starting material is relatively dilute (0.01 to 0.5 g of Mab/litre). However, if the hybridomas are immobilized in hollow fibers or by encapsulation, for instance, the monoclonal antibody is more concentrated--in the range of 0.1 to 10 g/litre). The large range of productivities depends not only on the production method but also on the productivity of individual hybridoma cell lines. The use of the cell culture technique for scale-up of the production of Mabs as well as the problems and techniques for recovery and purification were addressed by the speakers at this conference.

Production and Recovery of MABS Produced in Airlift Reactors

Research in the efficiency of airlift reactors for scale-up of Mabs production was started at Celltech Ltd. (Slough, UK) about 6 years ago under a UK government initiative to produce Mabs against blood group substances. Celltech's A. Kenney discussed the work carried out by them. He and his group found that hybridoma growth in suspension *in vitro* was necessary for scale-up production. Furthermore, they found that the airlift reactor was superior to conventional turbine-agitated reactors. The advantages are:

- Simple design (no moving parts)
- Effective mixing and mass transfer characteristics combined with low shear
- Behavior predictable in terms of mass transfer and mixing over a range of scales.

Kenney and his group also developed a computer model to predict what happens during scale-up. A series of scale-ups were used starting with 10 litres + 100 litres + 1000 litres. The cells were separated, concentrated, and Mabs purified from the final 1000-litre bioreactor. A serum-free medium for culture of hybridoma cells was also developed at Celltech.

At the present time, Celltech has a new facility at Slough in which airlift reactors are used for large-scale production of Mabs. The setup was designed to meet product safety requirements for products for human use. The purpose-built facility is computer controlled. Antibody production is at levels of 40 to 500 mg/litre. The variation in yields is due to the fact that there is a variation in the

amount of antibody produced depending on the specific antibody. Kenney stated that, at present, Celltech is the largest producer of Mabs for commercial use and has 40 to 50 different cell lines obtained from laboratories all over the world.

Recovery of the desired product (Mabs) involves three stages: (1) clarification, (2) concentration, and (3) high-resolution purification of Mabs. For the recovery of Mabs from the 1000-litre airlift fermenter, Kenney adds a flocculent which is removed with cell debris by centrifugation. The clarified supernatant is then concentrated 5- to 20-fold using sterile hollow-fiber filters in which a membrane retains larger molecules while smaller molecules (such as water and salts) are removed. For high-resolution purification Kenney uses immunopurification with immobilized protein A, a staphylococcal protein with high affinity for immunoglobulins. Kenney stated that a high degree of purification is obtained in one step with a high yield which is usually quantitative and predictable. It is a hygienic operation--i.e., easy to keep clean because only a single step is required. The procedure is now automated (operator independent) and therefore reliable and reproducible. Kenney also uses small protein A affinity columns automated to be used in sequence because this is much cheaper than one large protein A 500-litre column. The protein A columns in sequence can be used for 100 cycles before replacement.

Kenney emphasized that the quality of Mabs for therapeutic application is extremely important. The product quality issues that must be checked are:

- Viruses
- Host cell DNA
- Nonantibody protein
- Removal of process material
- Pyrogens.

Product quality controls are:

- Cell banking (sterility, stability)
- Process validation (for example, clearance studies)
- Analytical methods (DNA, nonantibody proteins, retroviruses)
- In-process monitoring (for example, use of reverse transcriptase for retroviruses)
- End-product quality control analysis (sodium dodecyl sulfate polyacrylamide gel electrophoresis, isoelectric focusing).

Checks for viral contamination include:

- Cell banking (virus testing)
- Process validation (virus clearance)

- In-process monitoring
- Final product testing.

Host cell DNA contamination is checked by:

- Analytical methods (hybridization essay)
- Process validation
- Final product testing for DNA.

The final products are tested for:

- Potency
- Identity
- Purity
- Sterility
- Pyrogens.

At present Celltech is working on scaling up the production of Mabs to even larger amounts--1 kilogram batches. Kenney and his group are also investigating continuous operation on this very large scale as well as ways to improve cellular productivity. The latter involves genetic and physiological studies. Another Mabs production problem being studied is that the degradation of Mabs varies. For most Mabs there is little or no degradation of Mabs by the Celltech methods, but with some Mabs there appears to be appreciable degradation. The degradation products can be eliminated by ion-exchange chromatography to a large extent but Celltech is investigating other procedures. Kenney also stated that the UK government limits on allowable protein A contamination of Mabs are, at present, 15 parts per million. However, if large doses of Mabs are used therapeutically in humans, this level may be too high. Therefore, another area being investigated is the reduction of protein A contamination.

Growth of Hybridomas and Secretion of Monoclonal Antibodies *In Vitro*

The problems encountered in large-scale growth of hybridoma cells in culture and the different procedures used for downstream processing of Mabs were discussed by N. Emery (Department of Chemical Engineering, Birmingham University, UK). Emery stated that the kinetics of hybridoma growth have to be carefully evaluated because the more rapidly the antibody (Ab) is produced, the more rapid is the loss of viable cells. Therefore, the conditions of hybridoma growth must be adjusted so that one obtains a relatively high level of Ab production with minimal loss of viable cells. Most of the Ab production takes place in the stationary phase of the hybridoma cell culture. However, there is considerable variation between different laboratory groups and different systems with respect to Ab production and cell death. It appears that cell death is not due to ex-

haustion of limiting nutrient but rather is a problem of accumulation of intermediary metabolites (lactate, glutamine, ammonia, etc.). The response of the cells to these intermediary metabolites varies from negligible to the extreme response of cell death. The Birmingham Cell Line developed at the University of Birmingham is quite resistant to these intermediary metabolites. However, Emery and his group also investigated amino acid pools (alanine, ornithine, and citrulline) which did accumulate during cell growth. These amino acids were found not to be a problem but rather the accumulation of relatively large molecular weight toxic products (1 to 10 kilodaltons). Emery and his group use ultrafiltration (hollow fiber filter system) for concentration and initial purification of the secreted Mabs produced by the hybridoma cell cultures. He stressed that the transport of products into and out of the hollow fiber system is important and must be studied and carefully controlled.

Emery then discussed bioreactor design/operation options. One method used is batch operation of fully suspended cells. This may be simple batch operation, fed-batch (volume maintained constant), or fed-batch (varying volume). He thinks that one of the handicaps of airlift reactors is the difficulty in dealing with variable volumes in the fed-batch system used in airlift reactors. Another type of reactor system is the chemostat system using suspended cells. The advantage is that one is able to examine the conduct of cells during different growth rates. The limitations are that the chemostat produces a constant flow of product at constant concentration but the kinetics are adverse. In the perfusion system, either a continuous or batch operation can be used. There is retention of cells by some mechanical means such as a fine mesh screen--the cells and products formed are selectively retained. The retention systems can be made selective for various components. For cells alone, there are variations of the spin-filter technique using ceramic cartridges or immobilization. Hollow fibers which selectively retain cells and products can be used or flat membranes (Millipore Co.) or microencapsulation (Danon Co.). The ideal cell-retaining membrane properties are: elimination of large-molecular-weight toxic products, retention of Ab, and removal of small molecules by diffusion. Emery and his group use bundles of hollow fibers, called Fiberfirm, with medium retention. They obtained a 3- to 4-fold improvement in Ab titer with this system but are now investigating a loop system with Millipore filters of different types to

ascertain if this system will lead to an increase in recovery of Ab.

Emery then discussed the types of hybridoma cell cultures used for Mabs production. These are: (1) monolayer (5×10^5 to 2×10^6 cells/mL), (2) suspension (5×10^5 to 10^7 cells/mL), and (3) dense (7×10^8 cells/mL). The reactors used for monolayer cultures are roller bottles or microcarrier static beds; for suspension cultures, stirred tank or airlift reactors; and for dense cultures, entrapment in an inert fibroid matrix. Emery thinks that the dense cell cultures system have the following advantages:

- Smaller reactor volume
- More concentrated product
- Earlier separation
- Higher recoveries
- Smaller equipment needed for separation of product.

They also give the possibility of a higher specific activity of the final, purified Mabs as well as easier separation, cheaper media, and more reproducible productivities. The disadvantages of dense cell cultures are:

- Greater difficulty in scale-up
- Oxygen transfer problems
- Physically more complex reactor design
- Higher degree of control required
- Additional processing steps may sometimes be necessary, depending on the type of Mabs.

Emery thinks that more research must be done, comparing the different systems to find the best and most efficient one.

Nutrition of Hybridoma Cells

A review of nutrient requirements and factors influencing cell growth of *in vitro* cell cultures in general and that of hybridoma cells in particular was presented by M. Butler (Department of Biological Sciences, Manchester Polytechnic, UK). During the growth of hybridoma cells in culture, a stoichiometric conversion of glucose to lactate occurs in the Manchester hybridoma cell line used by Butler and his group. Lactate and ammonia produced by this reaction appear to be two important inhibitors of hybridoma cell growth and viability. About 25-mM lactate as well as 2- to 5-mM ammonia are produced in the hybridoma cell culture, which can be toxic to the cells. One of the basic problems is that most cell culture media are overloaded with nitrogen. Thus, these investigators substituted glutamic acid for glutamine in the culture medium to decrease the ammonia production.

They are also investigating the removal of ammonia by enzymatic or immobilized cell systems. Butler emphasized

that the amino acid content and composition in the medium was an important factor in efficient cell growth and that it is necessary to understand the amino acid balance of the cells in order to devise the correct balance of amino acids in the culture medium. Fetal calf serum (FCS) is used as a supplement in the culture medium. FCS poses several problems in that there is contamination by components of the FCS such as albumin, transferrin, and immunoglobulins derived from the FCS. In addition, growth factors and hormones may also be contaminants from the FCS. Furthermore, proteolytic enzymes from the FCS can cause Mabs breakdown. The hybridoma cell lines themselves may also produce proteolytic enzymes, and FCS may serve to inhibit, rather than cause proteolysis, in some circumstances. Therefore, monitoring separation by electrophoresis should be used to indicate when protease inhibitors may be necessary. Many hybridomas can be adapted to grow in serum-free (not protein-free) culture thereby simplifying purification. However, the risk of reduced productivity of the cells and the high cost of serum-free media mean that, at present, the majority of Mabs are still being produced using FCS-supplemented medium. Butler thinks that a systematic study of the culture medium is very important and much work still has to be done to develop the best culture medium for hybridoma cells.

Immobilized Cell Culture Systems

One of the procedures used for large-scale production of Mabs for commercial use is the immobilization of cells in the bioreactor. This topic was discussed by C.A. Lambe (Biotechnological Group, Harwell Laboratories, Oxford, UK). Lambe addressed the use of immobilized animal cells for the production of compounds for diagnostic and therapeutic purposes. Some of the compounds produced by animal cells are hormones, antigens, antibodies, human proteins, growth factors, pheromones, and Factor VII from human blood. If the immobilization can be carried out at high cell density, one advantage is that the cells can be reused. Other benefits are:

- Retention of catalyst
- High biological activity
- Microenvironmental control
- Uncoupling of growth and production (a most important point because in standard fermentation procedures this does not occur).

With immobilized cells, the biomass remains constant, maintaining viable cells which leads to greatly increased production of the desired product. Other

advantages of cell or enzyme immobilization are:

- Increased concentration of biocatalyst in the reactor vessel
- Improved contact between the mobile and starting phase.

Two main methods for cell immobilization are adhesion (microcarrier) and entrapment in inert matrix. To maximize the production of a desired compound using an immobilized cell bioreactor, a maximum volumetric loading with close packing of 10-micron spheres coated with the cells is required. According to Lambe, 52 percent of the reactor volume should be occupied by the cells. If the cells are encapsulated (packed within the spheres), 27 percent of the bioreactor volume may be occupied by the cells. However, there is the problem of a practical limit to encapsulation as, in general, only about 12 percent of the bioreactor volume is occupied by the cells. Lambe and his group use immobilized cells not only for the production of Mabs (hybridoma cells which produce Mabs are animal cells) but also immobilized animal cells for the production of hormones, growth factors, etc. The immobilized cell system used by these investigators is a continuous bioreactor system which utilizes a recycling loop from the medium and a product withdrawal loop. They have a special type of immobilization matrix which is highly permeable to larger molecular weight molecular species and has excellent long-term stability. The system is now in the scale-up process for commercial production of Mabs as well as other products for diagnostic and therapeutic purposes. In this system, 70 percent of the cells at a given time are secreting Mabs. Lambe could not give any specific information about their matrix for cell immobilization because there is a patent pending.

Affinity Purification of Monoclonal Antibodies

For the intermediate stage of the downstream processing of Mabs there are three techniques suitable for large-scale purification of monoclonal antibodies: affinity chromatography, ion-exchange chromatography, and adsorption chromatography. The use of affinity chromatography was discussed by H.A. Chase (Department of Chemical Engineering, University of Cambridge, UK).

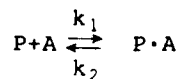
Affinity chromatography is based on highly specific interactions between an immobilized ligand and the substance of interest. For Mabs either the specific antigen-antibody interaction or the affinity of staphylococcal protein A for immunoglobulins can be exploited. The

sources of material for affinity chromatography following an enrichment step are: (1) ascites fluid, (2) fermentation mixture, or (3) supported (immobilized cells). The degree of purity required depends on the final use of the product. For diagnostic purposes, the degree of purity is not too important but for therapeutic purposes, purity is essential. According to Chase, fixed-bed affinity separation (affinity chromatography) is the desired method for three reasons: (1) high degree of purification can be achieved in a single step, (2) it is easy to scale up from laboratory separation to commercial application, and (3) it is straightforward to optimize and to automate.

The design of the affinity adsorbant must take into account the choice of the affinity ligand and choice of support matrix. The methods available for affinity adsorption of Mabs are use of: (1) immobilized antigen (molecule against which antibody is raised), (2) immobilized antibody (Ab) which is either Ab-class specific or antigen-binding-site specific, and (3) immobilized protein A (a general method, but success depends on the type of Ab).

The use of immobilized antigen poses problems in that it is expensive and availability may be limited. In addition, the antigen-antibody complex is often very strong, and the recovery of antibody may require rather harsh elution conditions which are likely to compromise the antibody activity or disrupt the covalent bond linking the ligand to the matrix--resulting in elution of the entire complex. The material generally used for immunosorbent chromatography is cyanogen bromide-activated Sepharose 4B. If antigen or anti-immunoglobulin antibody is bound to the column the adsorbent is unstable. However, cross-linking, for example, with glutaraldehyde renders the adsorbent stable and one can obtain a fairly pure product.

Chase pointed out that a single equilibrium model can be used for describing adsorption interactions.



(adsorbed complex) where P=protein, A=adsorbent. The dissociation constant

$$K = \frac{k_2}{k_1}$$

gives an isotherm relationship of protein in solution and amount of protein adsorbed. The higher the concentration of

protein in solution, the more is bound. The capacity of the column bed also has to be determined. There is usually some loss of antigen but it generally amounts to only about 10 percent. Using a human IgG/protein A model system, Chase examined the effect of the degree of protein A loading and the effect of adsorption (washing) buffer. The binding buffer may offset binding to some extent, but this is not too important according to Chase. In order to decide on the size of the column bed one assumes that the size of the bed is proportional to the amount of material processed per cycle and the cycle time is independent of bed size. Then the number of cycles needed is proportional to bedsize^{-1} and the total processing time is proportional to bedsize^{-1} . In evaluating adsorbant costs one can figure that if the adsorbant is stable then the cost involves only the bedsize; if it is labile, then the cost consists of bedsize times the number of cycles.

Chase and his group think that affinity chromatography is the preferred method for intermediate and in some cases final purification of the product (e.g., Mabs). However, as described above, there are many factors to take into account in deciding about the materials and conditions to be used. Different types of Mabs exhibit different behaviours on affinity purification so the conditions must be determined for each type of Mabs. There is no system which is universally applicable.

Conclusions

The large-scale production of monoclonal antibodies (Mabs) has been pioneered by small, competing biotechnology companies such as Celltech Ltd., which is now one of the major producers of Mabs. Although scale-up of Mabs is being carried out by several industrial concerns there is still room for improvement of the methodology. It appears that the culture of hybridoma cells in nutrient media *in vitro* is the preferred starting material for large-scale production of Mabs, but there is still a need to optimize the system and several possibilities for this were raised by the speakers. Downstream processing, which can be divided into three stages--initial enrichment, intermediate purification, and final purification--was also addressed. Again, although there are several approaches, new ideas are being investigated for further improvement. The speakers were all from the UK (academic and industrial sectors). The presentations showed clearly that UK scientists are dealing imaginatively and thoroughly with

the improvement of methods for scale-up of Mabs production for commercial use.

2/05/87

Material Sciences

CRYSTAL GROWTH UNDER MICROGRAVITY CONDITIONS

by Louis Cartz. Dr. Cartz is the Liaison Scientist for Materials Science in Europe and the Middle East for the Office of Naval Research's London Branch Office. He is on leave until June 1988 from Marquette University, College of Engineering, Milwaukee, Wisconsin.

The 6th European Symposium on Material Sciences Under Microgravity Conditions was held from 2 through 5 December 1986, in the Parc des Expositions, Bordeaux, France, at the same time as the International Exhibition "Technospace."

The Technospace exhibition was set up under rather luxurious conditions with all the displays meeting the highest degree of exhibition standards. All space subjects were covered from rockets, satellite uses, space sensors, electronics, and related accessories. Several American firms and agencies were represented along with those from France, Belgium, Japan, and West Germany.

The Symposium consisted of many invited papers, as well as contributed papers and posters. Sets of abstracts were published by ESA and the complete proceedings were expected to be published in early spring 1987, by ESA Publications (reference number ESA SP-256). Sessions were organized on Critical Phenomena, Fluid Physics, Glass, Melt, Solution and Vapor Growth, Space Instrumentation, and Transport Phenomena. The important effects of convection current, diffusion rates and surface energy, on crystal growth were considered and discussed in a very large number of papers and it is this topic which effectively dominated the bulk of the presentations at the meeting and which I will review. A special note: Many authors used the abbreviations of "1 g" and " μg " to represent gravity conditions at the earth's surface and microgravity in space. I consider this is a most unfortunate and incorrect usage; I will use "G" and " μG ."

Crystallization From Solution Under Normal Gravity

An excellent review paper was given in French by B. Simon, J.M. Cherel, and P. Haldenwang (Université de Provence, Marseille, France) which described very elegant yet simple experiments of crystallization from solution under G; these experiments demonstrated very clearly the effect of convection currents on crystalline perfection. During crystallization from solution, the crystal and the solution do not have the same chemical composition. Simon et al. demonstrated the effect of convection (see Figure 1) by comparing the velocity of crystal growth under conditions with convection (a) and with reduced convection effects (b). This was accomplished by using thin vertical tubes to feed the crystallization solution to the growing crystal. When the growing crystal was situated at the top of the thin tube, there was a stable solution concentration gradient and diffusing became the principal mechanism permitting crystal growth; this is case (b). When the growing crystal was situated at the bottom of the thin tube, convection effects can occur as well; this is case (a). The rate of crystal growth in case (a) with convection is very much greater than in case (b). Simon et al. considered the case of ionic crystals in systems where no solid solution occurs, such as NaClO_3 and $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$, and described how the change of density of the solution with crystal growth results in a vertical convection current across the faces of the crystal. They calculated the Rayleigh number (Ra) for the fluid flow from the growth rate. At low Ra (10^8) there is laminar flow but as the solution density decreases progressively by flowing over the vertical crystal faces, the Ra increases (10^{11}) and turbulent flow occurs. This results in growth steps and growth ridges parallel to the fluid movement. Simon showed several precise and elegant examples of these effects where the resulting crystal is highly imperfect. Simon et al. were able to observe the turbulent flow around the crystal from the density differences in the solutions, and obtained good agreement with their calculations of Ra number and the consequent laminar or turbulent flow. They could then relate directly the turbulent flow to the growth defects in the crystal. Moreover, the presence of growth steps on the crystal faces could affect the turbulent fluid flow so that the final crystal morphology could be dependent on the orientation of these growth steps in the gravity field.

The work of Simon et al., demonstrated very clearly the effects of convection on crystal growth and hence indica-

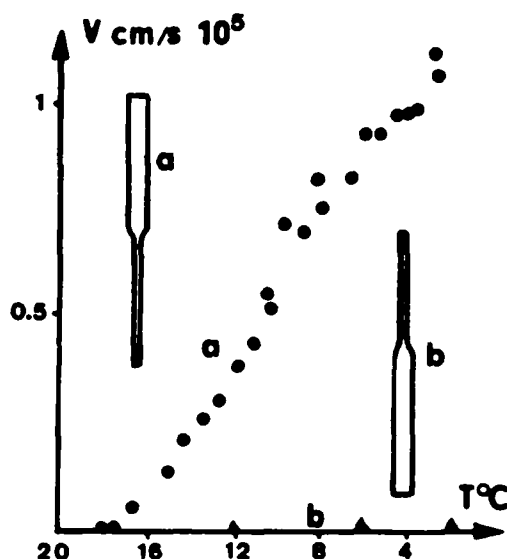


Figure 1. Crystal growth rates of NaClO_3 : (a) with convection, (b) with diffusion only. The growing crystal is at the top (case a) or bottom (case b) of a thin tube. The solution is saturated at 20°C (see text).

ted the advantages to be obtained if the convection currents could be avoided by removing the effects of gravity. Under μG , the Ra is expected to be $\sim 10^8$, resulting in uniform convection current with laminar flow and thus avoiding the turbulence which results in crystal morphological imperfections and changes.

Crystal Growth Under Gravity and Microgravity

M.C. Robert and F. Lefauchaux (Laboratoire de Minéralogie et Cristallographie, Paris, France) gave an excellent presentation of crystal growth from solution under G and under μG . They considered the supersaturation necessary for precipitation and crystal growth to occur. The width of this metastable supersaturation-concentration temperature-zone depends on the material under crystallization, on solution agitation, and on the solution viscosity. A narrow metastable region can lead to parasitic nuclei at the expense of the desired crystal. They described experiments with potassium aluminum sulphate, starting from a seed crystal and subsequently examining slices of the crystal to observe striations and growth bands. They showed how the orientation of these striations, etc. depended on the direction of the convection currents. The presence of dislocations, for example, can increase the growth rate by an order of magnitude, which results in changes in crystal morphology and in

physical properties (for example, the dielectric response of PbHPO_4 depends on crystalline perfection).

They discussed the various methods of reducing the effects of convection: isodensity, viscous, configurational stabilization, and microgravity systems. I will discuss the pertinent points of each.

1. Isodensity systems where $d\rho/dc=0$ (ρ density, c concentration) for some solute/solvent pairs, such as thymol/diethyl carbonate where $d\rho/dc$ is 10^{-5} g/cm³/weight percent. Difficulties still arise due to the heat of crystallization resulting in a local temperature gradient.

2. Configurational stabilization systems with the growth interface in a horizontal cell and also one-dimensional configurations. There is still the trouble of parasitic nucleation.

3. Viscous Systems. It is difficult to find additions to increase the viscosity of solutions without changing the solubilities of the solute. However, one example is the addition of polymethylmethacrylate to an aqueous solution of KNO_3 . The use of gels is well known and crystals grown using small amounts of gel can be nearly dislocation-free with growth bands suppressed (e.g., $\text{Ca}_3(\text{PO}_4)_2 \cdot 2\text{H}_2\text{O}$ from aqueous solution). The disadvantage of increasing the viscosity of systems is contamination by the gel and the fact that there are very few known agents for high temperature or non-aqueous solvents.

4. Microsystems. Using very thin systems, for example, between two microscope slides less than 500 μm apart, very fine crystals of Pb nitrate phosphate have been grown.

5. Microgravity. In space experiments, a three-compartment device with temperature control can be used, where the end cells contain the ingredients A and B and these are permitted to mix in the middle cell. The crystals that have been grown in μG were listed by Robert et al. in their paper along with the maximal size achieved; the references will be given in the published proceedings. Trouble is experienced on reentry; an imperfect growth layer was found about the crystal when the crystals were examined by both x-ray topography and holographic methods.

Silicon Crystals Under Microgravity

A. Cröll, W. Mülles and R. Nitsche described experiments under μG on Si crystals and discussed the difficulties in viewing opaque systems. For Si the concentration of the dopant can be determined from conductivity measurements, but

the concern is the distribution of the dopant throughout the crystal, which depends on diffusion of the dopant and also on convection within the melt. By diffusion only, the concentration of the dopant is expected to be constant throughout the solidification of the Si except at the beginning and end of the solidification process. However, by perfect mixing or by convection, the concentration of dopant in the crystal increases with the fraction solidified. This gives rise to macrosegregation while microsegregation arises due to turbulence (high Ra number) which gives rise to striations and other growth defects. For the μG experiments, striations are observed on crystals due to the reentry phenomena. An experiment in μG used free surfaces, floating zone (FZ) techniques with optical heating. Subsequently the crystals are cut, polished, and etched to display the crystal perfection.

Cröll et al. presented results of several space flight experiments. The origin of inhomogeneities of the order of 1 μm are now understood to arise due to surface energy Marangoni flow. These have been successfully suppressed using surface films. For Si, a film of SiO_2 is deposited, resulting in striation-free crystals. The thickness of SiO_2 is about 7 μm , this being reduced by the reaction of the molten Si to form SiO; however, the surface layer can be considered to be approximately stable during the FZ melting.

Cröll et al. described their dopant injection experiments during FZ. The dopant B at one point on the Si melt surface diffuses as the FZ progresses along the crystal. The dopant distribution is found to correspond to pure diffusion transport of B when Marangoni convection is excluded, otherwise the B distribution corresponds to the total-mixing case. By comparing G and μG experiments, Cröll et al., detected an additional buoyancy flow in the case of G experiments.

Other Presentations of Interest

P. Pant (Krupp Forschungsinstitut, Essen, West Germany) described the MnBi system, which has a liquid miscibility gap. The intermetallic compound MnBi is ferromagnetic and forms peritectically at 445°C. Under G, on cooling a melt of MnBi, the yield of MnBi is less than 20 percent, due to the separation of liquid Mn from liquid Bi on cooling through the miscibility gap. During a μG experiment, the MnBi was melted at 1150°C and cooled at 6.7 K/s. The resulting MnBi was distributed uniformly throughout and the yield was 30 percent. The magnetic coercivity factor of this solid obtained in the μG experiment was 5 times greater

than that obtained in the G experiment. During another μ G experiment, the MnBi was also heat-treated from 450 to 470°C for 60 to 180 minutes, when 50 percent MnBi of large crystal sizes was formed. Pant described how the amount of MnBi can be further increased to 95 percent weight by subsequently extruding at 220°C the solid obtained from the μ G experiment.

V. Braesch and G.H. Frischat (Technische Universität Clausthal, West Germany) described the homogeneity of the crystallization process of $\text{Li}_2\text{O-SiO}_2$ and $\text{Na}_2\text{O-B}_2\text{O}_3\text{-SiO}_2$ glasses under G and under μ G melting. The crystallized glass formed at μ G is much more homogeneous due to fewer heterogeneous nuclei from the container walls being transported into the bulk of the melt by buoyancy convection. The addition of PtCl_2 as a nucleation agent leads to a very uniform fine-grained microstructure in the μ G specimens. Attempts have been made to eliminate the effect of the container walls for G experiments by using nonwetting walls such as carbon.

The crystallization of bulk metals was described by several workers. No general review of the subject was presented but only several specialized studies. J.D. Hunt (Oxford University, UK) described planar, cellular and dendritic growth fronts during the cooling of melts. The type of growth front depends on the heat flow at the interface and perturbations. Numerical calculations of the spacings of the dendrites include a supercooling term, temperature gradients, the velocity of the cooling front, and surface energy effects.

The supercooling of the bulk metals using electromagnetic levitation techniques was described by R. Willnecker, D.M. Herlach, and B. Feurerbach (Deutsche Forschungs- und Versuchsanstalt für Luft- und Raumfahrt [DFVLR], Cologne, West Germany). Fe-Ni and Cu-Ni alloys of all compositions have been supercooled--350 K in the case of the Fe-Ni alloys--in the absence of container walls by electromagnetic levitation. However, the heating and the magnetic effects need to be separated. Spheres up to 6 mm in diameter have been levitated in this manner with careful positioning of the magnetic field to overcome temperature variations, and using cooling gases. Wilmeder et al. stated that this is restricted to high m.p. metals, but this was questioned by some speakers. The supercoolings have been measured for Ni, Cu-Ni, Cu, Fe and Fe-Ni. Willnecker et al. have studied in detail the Fe-Ni system and have noted that the supercooling curve follows the shape of the liquidous curve for the Fe-Ni system.

D. Camel et al. (Centre Énergie Nucléaire Grenoble [CENG], Grenoble, France) compared experiments under G and also at μ G on Al-Cu alloys with 1-, 26-, and 40-wt percent Cu. The dendritic growths and their spacings, and also columnar growths, depend on the solution concentration gradients as well as thermal gradients; the μ G samples are free from macrosegregation effects.

The cellular solidification of Pb-Te alloys in μ G was presented by B. Billia et al. (Faculté des Sciences St. Jérôme, Marseilles, France) and compared with experiments under G. During the space mission D1, three alloys containing 25-, 30-, and 40-wt percent thallium were solidified using 6 thermocouples to measure the thermal gradients with time. After solidification, the microstructure and chemical analysis of thin slices showed macrosegregation effects with only small differences between G and μ G conditions. There were many growth patterns, but they were not easily explained.

H. Hanache and R. Jilg (DFVLR, Cologne) gave a very careful analysis of the reduced gradient field aboard an orbiting spacecraft that could affect some physical process. Accelerometer systems were included during some missions near the center of gravity of the craft; they showed that:

- Firing during the mission could induce values of 10^{-3} G
- An astronaut's hopping, induced 10^{-2} G where the natural frequency of the craft was about 5 Hz
- Opening an experimental drawer on the craft caused an acceleration comparable to 10^{-2} G
- Drop, sled, and quiescence experiments were also carried out.

For future experiments, careful training of the astronauts is required.

The Panel Session on Crystal Growth

A special panel session on the crystal growth posters was chaired by R.F. Sekerka (Carnegie-Mellon University, Pittsburgh, Pennsylvania), who raised a series of well-chosen topics. The first poster-discussion involved the influence of side walls on solution convection. R.Z. Guerin et al. (Faculté des Sciences St. Jérôme) calculated the Ra number for lateral, rigid, insulating boundaries with directional solidification as a function of gravity, a solute segregation coefficient, and the aspect ratio $\beta = WV/D$ where W is the distance between the walls, V the growth rate, and D the solute diffusion coefficient. At large β , corresponding to approximately 30 boundary layer widths, Ra approaches

the limiting value for an infinite medium.

A discussion was held of the work of G.H. Otto and G. Froberg (DFVLR, Cologne), who examined the dissolution kinetics in the miscibility gap of Ga-Hg in μG . X-radiographs recorded in-flight, stationary Hg droplets of diameters 0.2 to 1.2 mm, the Ga being relatively transparent to x-rays. The temperature was then raised at 10 K/min above the miscibility gap and then the two phases became one phase with the Hg dissolving into the Ga. At a microgravity level of 10^{-4} G this should have been governed by diffusion with no convection processes. However, the results do not agree with calculations based on diffusion alone. Some speakers suggested Marangoni convection; others questioned the validity of the diffusion coefficient used. When the same experiment is carried out under G, the Hg droplets separate too fast due to the difference of density between Hg and Ga.

Conclusion

There were so many different facets to this meeting that only a few could be covered by this selective article. Consider, for example, the invited papers, which included: "Morphological and Convective Instabilities in Microgravity" (R.F. Sekerka, Carnegie-Mellon University); a review of Japanese work by A.B. Sawaoka et al., NASDA, Japan; "Crystal Growth from Vapors" (F. Rosenberg, University of Alabama); "Bénard-Marangoni Instabilities in Fluids" (M.G. Velarde, U.N.E.D. Madrid, Spain); "Array Growth of Cells and Dendrites" (J.D. Hunt, Oxford University, UK); "Gravity and the Growth of Crystals from Solution" (B. Simon, Université de Provence, France) and a similar paper by M.C. Roberts et al. (Université Pierre et Marie Curie, France); "Dopants in Silicon Crystals Under Microgravity" (A. Cröll et al., Universität Freiburg, West Germany); and "Protein Single Crystal Growth" (W. Litke, Universität Freiburg, West Germany).

Several crystals have been grown in relatively short periods of time under μG with markedly reduced imperfections; the talk of Robert and Lefauchaux well illustrated and reviewed this. The very fine discussion of Simon, Cleavel, and Haldenwang defined very clearly the problem of obtaining perfect single crystals due to the convection flow of depleted solution over the crystal faces. Perfect crystals are needed for measurements of physical properties. To obtain perfect crystals various methods were proposed: (1) Surface coatings have been shown to suppress Marangoni effects-- SiO_2 on Si in particular; (2) increased viscosity of the crys-

tallization solution using polymers or gels; (3) one-direction flow avoiding convection by using sets of capillaries, membranes, or other restrictive arrangements; and finally, (4) there should be an advantage in using very, very slow growth rates.

The experiments in space under μG condition produced interesting crystal growth results and also indicated the parameters that need to be controlled under G conditions if the perfection of crystals grown is to be improved under the earth's gravity.

A short review of the Bordeaux meeting and exhibition appeared in *Le Monde*, 10 December 1986. It reported that a private organization "Intospace" has been set up to promote the industrial use of microgravity and is supported by several French firms (Aérospatiale, Baikowski Chimie, Bioeurope, Matra, Michelin, Pechiney, Rhône-Poulenc, Sacilor, and la Société Européenne de Propulsion).

2/24/87

THE FRENCH SOCIETY OF METALLURGY

by Louis Cartz.

The Société Française de Métallurgie (SFM) held its autumn meeting from 14 through 16 October 1986 in the rooms of Les Ingénieurs et Scientifiques de France (ISF), Paris. This well-organized meeting was attended by over 200, almost all of whom were from France, with just a few from the French speaking countries of Belgium, Switzerland, Luxembourg, Algeria, Morocco, and Tunisia. All of the proceedings were in the French language. SFM holds several meetings each year, and the abstracts are published in advance in the *Revue de Métallurgie*. The abstracts of the October meeting are in No. 9, September 1986, pages 400-494 (in French).

The president of SFM, Professor Hocheid, opened the meeting, introducing the four special topics chosen. The four topics of the meeting and their organizers were:

1. Determination of Equilibrium Diagrams (C. Bernard, Laboratoire de Thermodynamique et Physicochimie Métallurgique [LTPCM], École Nationale Supérieure d'Électrochimie et d'Électrometallurgie [ENSEEG], Grenoble).

2. The Behavior of Welds (M. Bramat, Institut de Soudure, Paris).

3. The Treatment of Metals by High-Energy Beams (A. Traverse, Laboratoire de Spectrométrie de Masse, Université de Paris Sud).

4. Recent Developments in Metallurgy (R. Lallement, Institut de Recherche et Développement Industriel [IRDI], Commissariat d'Energie Atomique [CEA], Paris).

Five separate sessions, programed for young metallurgists, were organized by B. Dubois, École Nationale Supérieure de Chimie de Paris (ENSCP) and H. Paqueton, Conservatoire National des Arts et Métiers (CNAM), Paris. The 20 papers presented at these sessions covered mechanical behavior, structure and physical properties, metals and nonmetallic materials, damage, and corrosion. Hocheid explained how one proposed topic, Plasma in Metallurgy, had to be abandoned because, he presumed, many of the studies were of a classified nature or because there were not many such studies in progress in France.

Treatment of Metals by High-Energy Beams

I will concentrate on the treatment of metals by high-energy beams, for which the invited paper was given by M.J. Grilhé (Université de Poitiers). Grilhé, who is director of the university's metal physics laboratory, gave an excellent review of this field. He considered the use of lasers, and electron and ion beams, discussing the improvements that can be obtained in corrosion resistance, hardness, friction, wear, and fatigue properties, and also of the surface changes that can be induced in magnetic, electrical, optical, thermal barrier, diffusion barrier, adhesion, and thermal expansion behaviour. The surface can undergo a wide range of structural modifications including amorphization, diffusion formation of carbides and nitrides, diffusion after metallizing with Al or other metals to form surface alloys, or the conversion of the surface by oxidation, phosphating, or using other reagents. Rapid development is underway in studies that combine chemical vapor deposition (CVD), with lasers, plasma, and laser-electron treatments. In his review, Grilhé did not give specific references, but it was evident that much of this work has, in fact, been carried out in Poitiers (Grilhé 1986); at least six representatives from Poitiers gave interesting papers later in the conference.

Grilhé reviewed the use of 100-keV to 1-MeV ion beams. A very large number of atomic displacements are created when ion beams are used; for example, a Kr^+ ion of 100 keV can give rise to about 500 vacancies, where the $dpa=10$ (displace-

ments per atom) within the first hundred Å of the surface layer. The quench rate $10^{12}^{\circ}C/s$ is much greater than by laser. The surface layer can undergo phase transformation, change of precipitate (ppt), amorphization, and ion beam mixing effects.

Grilhé gave some examples of ion implantation that might interest the metallurgist. Nitrogen irradiation of Al results in a ppt of AlN in epitaxy with the Al matrix (Denanot et al., 1985). Xenon implanted into Al results in a ppt of Xe in a solid form where the x-ray diffraction pattern has extra diffraction spots which demonstrate that solid Xe is present. The solid Xe can be explained by the internal pressure caused by the fact that the atomic volume of Xe is about three times that of Al (Templier et al., 1984, 1985a, 1985b). Metallurgical applications of implantation include, in particular, the implantation of N into steels, with wear properties being improved by a factor of 10. Such materials are marketed in France under the name IMPLANTEC by Groupe Usinor, Centre de Recherches d'Unieux [UNIREC]. Nitrogen implanted into Ti and P or B into Ni results in the amorphization of the surface and an increase of hardness. Grilhé said that the frictional properties of Mo and Sn are also reported improved by implantation but he gave no further details. Attempts to improve corrosion resistance have been less successful; the use of Y into Cr-steels has been reported. He believes that for catalysis, many private studies are investigating Pt implanted into Fe.

The limitations of ion implanting were listed by Grilhé to cover:

1. Only about 1000 Å are penetrated by most elements when using 100 keV ions; however, there is the strange fact that N penetrates much further and provides effects to much greater depths (though this process is not understood).

2. The length of time to carry out an implantation can be very long, particularly where it is necessary to avoid surface heating effects.

3. The sputtering effects of heavy atoms limit the level of alloying that can be achieved as well as causing surface erosion.

Grilhé described the use of higher energies in the MeV range and the phenomenon of ion beam mixing. Use is frequently made of multilayers to a total thickness of about 1000 Å. Thus Fe-Al alloys have been prepared by irradiating Xe^+ ions into alternate layers of Fe-Al. The very fast quench rate results in amorphous layers of $Al_{1-x}Fe_x$ alloys. This

method can overcome the limiting effects of sputtering so that higher concentrations can be achieved; repetition of the process enables thicker layers to be built up. Ni-Al (equiatomic) alloys have been obtained in this way using Xe (360 keV) at fluences up to 10^{16} ion/cm² at temperatures of 77 K and 300 K. The alloy formed at 77 K is amorphous and with vastly different electrical conductivity properties from those of alloys formed at 300 K. The alloys FeMg, FeAl, CoAl, NiAl have all been studied. The alloy system FeMg is normally immiscible but ion beam mixing does occur at 77 K.

Treatment of Surfaces by High-Power Lasers. M. Govin (Institut National des Sciences Appliquées, Villeurbanne, France) described the treatment of surfaces by high-power lasers. He pointed out that special surface treatments have to be carried out to avoid reflection of the laser beam energy from the metallic surface. The laser heats the first 10 to 100 nm of material. Melting, evaporation, and thermal shock result, along with the formation of a plasma that can return along the path of the incoming laser beam--and this plasma absorbs laser energy. A one-dimensional model has been set up to estimate the surface temperature; thermal conductivity, surface emissivity, ray size, and power of the laser are considered. Thus, a 3-kW laser with a ray cross section of 1 cm² can produce a temperature above 1000°C for steel, and internal stresses can result from the laser treatment. Govin discussed the potential uses of laser beam heating depending on the power density, fluence, scanning time, heating depths, and quench rates. Power densities from 10 to 10^{12} W/cm² are obtainable; quench rates are from 10^3 to 10^7 °C/s, and interaction times from 10^{-8} to 10^2 seconds with heating depths of 10^{-7} to 1 mm. Several useful combinations of laser power and scanning times can be defined for (1) shock hardening; (2) surface solidification by melting, grain refining, and vitrification; (3) depositions and surface alloying; and (4) surface hardening.

Treatment of Surfaces by a Continuous Beam of Electrons. M. Brenet (Centre d'Etudes Nucléaires Grenoble [CENG]), described the treatment by a continuous beam of electrons of copper and Cu/Cr, Cu/Ni, Cu/Al alloy surfaces. A beam of 15 kW, with a diameter of 0.3 mm is available, resulting in power densities of 10 MW/cm². He described the various scanning techniques and spot vibration methods to cover a precise area. Fine ppt with different microstructures are obtained, but the surface becomes non-flat--depending on the speed of scan and power in the beam--due to surface melting

effects and capillary action. Various microstructures can be obtained in the Cu alloy systems though the hardness properties are not always improved.

Ion Beam Mixing. Examples of ion beam mixing of Fe-Ti alloys were described by Brenier et al. (Département Physique Matériaux, Université Claude Bernard, Lyon I, Villeurbanne). Metallic glasses are formed which have not been obtained by extremely rapid liquid quenching techniques. Fe-Ti alloys are expected to exist in a noncrystalline or metal glass form based on the fact that metal glasses are generally obtained from metal alloys where the individual metals have different crystal structures (Fe is fcc and Ti is hcc), their atomic radii are very different, and where the enthalpy of formation of the alloy is small. Multilayers of Fe and Ti have been deposited on a Si(100) single crystal to a thickness of 200 nm. Irradiation of this system by Xe⁺ (800 keV) ions with 1.7×10^{16} ions/cm² at 77 K and 300 K produced Fe-Ti alloys that have been studied by Rutherford backscattering (RBS), grazing incidence x-ray diffraction, and Mössbauer and transmission electron microscopy. The alloys of Fe_{100-x}Ti_x have been studied over a wide range of compositions and for $29 < x < 66$ at 77 K, metal glasses are formed. The silicon substrate is found to be amorphous at 300 K yet crystalline at 77 K.

Papers Given in Other Subjects

Since there were three parallel sessions at the meeting, my selection of other topics is based on those papers presented at times other than those of the sessions of high-energy beam treatment of solids. Therefore, the following comments are necessarily limited.

Quasi-crystalline solids (QC) involving the icosahedral phase were reviewed by M. Dubois et al. (École des Mines, Nancy). He described how the subject has developed very rapidly since the work of Schechtman et al. (1984) in the Department of Materials Engineering, Technion, Israel. Many other compounds have been discovered with this structural arrangement. The crystallography of these compounds is still very much under discussion. Dubois reported on the AlMnSiFe and the AlMnCrFe alloys examined by x-ray and by neutron diffraction. The alloy Al₈₂Si(Mn_{1-x}Fe_x)₁₇ occurs with a QC structure with Fe up to 30 percent and, for the Cr alloy, with Fe up to 50 percent.

M. Vives et al. (Laboratoire de Magnétohydrodynamique, Université d'Avignon) described the crystallization features of molten metals in the presence of electric and magnetic fields. The experiment uses

a cylindrical electric furnace with a central cooling facility to induce radial cooling. The convection currents within the molten metal are normally determined by gravity but they can be determined by the electromagnetic field effects. Vives showed some very beautiful crystallization patterns with the crystals elongated in radial directions where the convection currents were no longer vertical but had been made to be horizontal.

M. Falk et al. (Laboratoire Génie Métallurgie, École des Mines, Nancy) have set up a model to permit heat transfer calculations of fusion fronts during electric arc melting of alloys of Ti and of Zr. M. Alexandre et al., also from Nancy, gave a very clear account of the sponge process for the purification of Zr using Zr-Mg-MgCl₂. The solid formed during the purification contains three separate parts, Zr in the form of nodules, Zr surrounded by Mg, and MgCl₂. Heating under vacuum leaves pure Zr in the form of a sponge, with 30 to 40 percent porosity. The heating-purification process has been studied by thermogravimetry and the stages of the sintering followed by scanning electron microscopy.

Conclusion

Many other papers were presented on the main topic of treatment of metals by energetic beams. There were also several posters. These papers and posters covered a wide range of topics:

- Metal hydrides, using H ion implantation
- Surface quenching by laser treatment of alloys of Zr
- Ti implanted by N
- Surface treatment of Ta alloys by intense laser beams
- Surface coatings by laser treatment of projected powders
- Localized recrystallization of Al alloys by laser or electron beams
- Surface amorphization of metal alloys by laser beams
- Amorphization of TiNi alloys by N irradiation
- Surface treatment of steels by laser
- Implantation of N in steels
- Ion beams mixing.

If you want further details of these studies, I will be glad to provide the abstracts and the names and addresses of the workers involved.

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2/24/87

Mechanics

FIRST INTERNATIONAL SYMPOSIUM ON DOMAIN DECOMPOSITION METHODS

by Eugene F. Brown. Dr. Brown is the Liaison Scientist for Fluid Mechanics in Europe and the Middle East for the Office of Naval Research's London Branch Office. He is on leave until September 1987 from the Virginia Polytechnic Institute and State University, where he is a Professor of Mechanical Engineering.

The First International Symposium on Domain Decomposition Methods for Partial Differential Equations was held from 7 through 9 January 1987 at the École Nationale des Ponts et Chaussées in Paris, France. The purpose of the meeting, partially supported by ONRL, was to bring computer scientists, engineers, mathematicians, and physicists together to discuss the theoretical and practical aspects of applying domain decomposition methods to the solution of structural mechanics, computational fluid dynamics, and reservoir engineering problems.

Twenty-six papers were presented at the 3-day meeting with almost half coming from the US. Among the European nations, France was the best represented with five papers. More than 150 people registered for the meeting with, as might be expected, the majority of attendees coming from France.

As the words imply, domain decomposition methods involve subdividing the original computational region into a number of subdomains and forming the solution to the original problem by re-collecting the subdomain solutions. The advantages claimed for domain decomposition methods are that they allow the use of different spatial discretizations (finite element versus finite difference), different orders of approximation (fourth order in regions of high gradients and second order elsewhere), different grids (structured versus unstructured), different algorithms (Runge-Kutta versus Lax-Wendroff), and different time-stepping schemes (implicit versus explicit) from one region to another. In addition they:

- Allow flexibility in the numerical modeling (in regions near a wall the Navier-Stokes equations could be used and the Euler equation used elsewhere)
- Permit an easy way to handle complex geometries
- Minimize the amount of in-core memory required
- Are very flexible in implementing local grid refinement
- Are well suited for implementation on parallel computers.

As repeatedly pointed out at the meeting, however, to take full advantage of domain decomposition methods, data transfer between the subdomains must be made as efficient as possible, otherwise domain decomposition methods are not competitive with global methods employing modern acceleration schemes such as multigrid and macrotasking.

Application of domain decomposition methods to finite element, finite difference, finite volume, and spectral methods were all presented during the course of the meeting. Finite element methods were given the most emphasis, however. This was due to the fact that domain decomposition has long been an important feature of these methods. In addition, the organizers of the meeting are themselves involved in the use of finite element methods and thus tended to invite speakers working in this area.

Finite Element Considerations

Among the speakers who concerned themselves with the mathematical aspects of finite element schemes were, from the US, G. Golub (Stanford University), A.T. Patera (Massachusetts Institute of Technology), M. Wheeler (Rice University), T. Hughes (Stanford University), O. Witlund (Courant Institute); from the USSR, M. Israeli, J. Pasciak, V. Agoshkov (Soviet Academy of Sciences); from France, J. Lions (Centre National d'Études Spa-

tiales, Paris), G. Murant (Centre d'Études et Dynamique, Villaneuve St. Georges), J. Periaux (Institut National de Recherche en Informatique et en Automatique, Rocquencourt); from Canada, M. Fortin (Université Laval, Montréal); and from Norway, P. Björnsdøl (University of Bergen).

It is important that the algorithm used for each of the subdomains be as efficient as possible. For finite element methods this demands that some type of preconditioning be employed. Preconditioning is a convergence acceleration technique which subdivides the coefficient matrix into a combination of a directly invertible matrix and a matrix which can be efficiently inverted by the process of iteration. The mathematical aspects of preconditioning were the subject of several papers including that of J. Pasciak (Brookhaven National Laboratories, New York) and T. Chan (University of California at Los Angeles).

Finite Volume and Spectral Applications

One of the most elegant applications of the domain decomposition method in the context of a finite volume solution was described by Professor J. Oppellstrup of the Royal Institute of Technology (KTH) in Stockholm, Sweden. He described the use of domain decomposition methods to solve the problem of transonic flow over the entire surface of a generic fighter aircraft. The fluid mechanics calculations involved the solution of the Euler equations by means of a finite volume, centered-difference, time-stepping algorithm due to Rizzi. A transfinite interpolation procedure with derivative and mesh size control was used to generate the computational grid. The flow domain was first decomposed into simple six-faceted supercells which were in turn divided into conventional, structured, finite-volume regions.

An application of the domain decomposition method to a spectral calculation was described by Patera. He showed a number of examples having remarkable resolution including: the flow past a cylinder, flow in grooved channels, and flow over a roughness element. Good agreement with measured heat transfer data was obtained. Patera has speculated that greater efficiency can be obtained from parallel processors if their geometry is matched to the configuration of the computational domain. For this purpose he has developed the concept of "Geometry-Defining Processors" (GDP's). These are microprocessors which are housed in manually reconfigurable physical geometric packages, which are aware of the parameters of these physical packages, and which are able to communicate this geometric

information, as well as numerical data, to nearest neighbors in a GDP assembly. Patera has produced GDP's in tetrahedral and wedge configurations and has interconnected them in a variety of configurations by means of infrared communication ports (see Figure 1). Eventually he hopes to build 1000 of such elements to investigate the practicality of this concept.

Finite Difference Applications

An application of the domain decomposition method to a finite difference calculation was presented by J. Flores of NASA, Ames. The objective of his calculations was to simulate transonic viscous flow over an isolated wing and a modified F-16A-like fighter geometry. In the isolated wing calculation, four domains were used in which the Navier-Stokes (thin-layer) equations were solved near the wing and the Euler equations were solved in the remainder of the flow field. The domains were overlapped and communication achieved by means of a linear interpolation scheme. For the Navier-Stokes equations an ADI algorithm (Pulliam and Chaussee, 1981) was used. To simulate the effect of turbulence the Beam-Warming turbulence model was used. For the isolated wing simulation approximately 150,000 grid points were used. The geometry was a NACA 0012 cross section having an aspect ratio of 3 and a 20° leading edge sweep. The Reynolds number was 8 million. Two cases were discussed, a Mach 0.826, 2° angle of attack case and a Mach 0.9, 5° angle of attack case. Both required approximately 45 minutes on a Cray X-MP/48 computer. The agreement with measured C_p measurements at inboard stations was good. Outboard on the wing, however, the calculations predicted a

zone of separation. Although the surface streamlines were found to be topologically reasonable from a qualitative point of view, the region of separated flow was much smaller than that observed experimentally. Further studies showed that this was probably due to a deficiency in the turbulence model used in the calculations. This contributed to poor agreement between the predicted and measured C_p values. Consequently, efforts are now underway to replace the Beam-Warming turbulence model with the Johnson-King model (Johnson and King, 1985), which has been found to perform well in separated flows. In addition, it was found that sharp gradients were sometimes lost across interfaces between a fine and a coarse grid region. To improve the performance of the algorithm, Flores suggested replacing the overlapped grids with abutted ones, for which an implicit conservative interfacing scheme would be used.

For the F-16A calculations, Flores used 300,000 points and divided the flow into 16 domains including special zones for resolution of the tip vortex and wing wake regions. For these calculations the Reynolds number was 4.5 million, the Mach number 0.9, and incidences of 1.7°, 4.4°, and 6° were investigated. Approximately 13 hours of Cray X-MP time was required for each of these calculations. The computed lift coefficients appear to agree reasonably well with the results of wing tunnel experiments conducted by General Dynamics. Future work involves developing a more realistic simulation of the flow around the inlet and tail section of the aircraft and the development of improved convergence acceleration techniques.

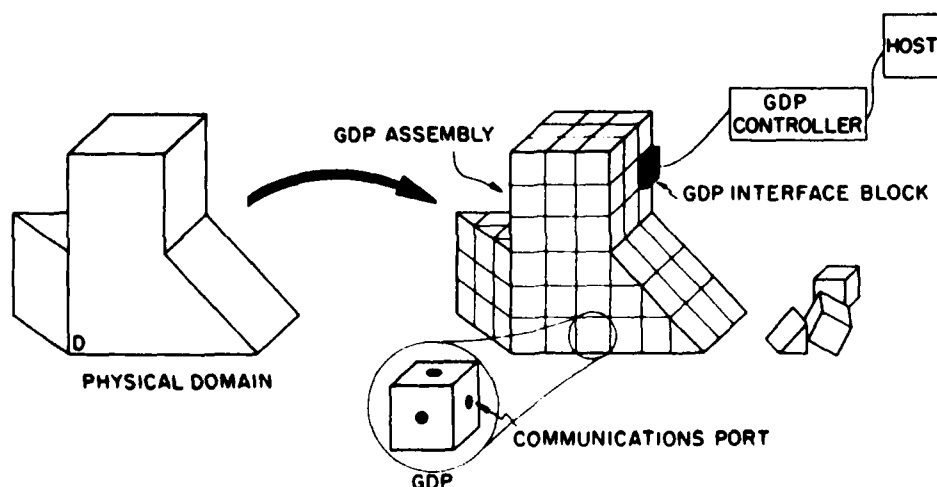


Figure 1. Assembled GDP's.

Another interesting application of the domain decomposition method to a finite difference calculation was presented by K. Gustafson of the University of Colorado in Boulder. His interest was the flow in a driven cavity which he modeled by means of the linearized vorticity transport equation. Using a combined ADI and multigrid technique he obtained a cascade of vortices in the corner of the cavity which extended down through multiple grid refinement levels. His computations supported Moffatt's (University of Cambridge) theoretical predictions in the corner but failed to substantiate Moffatt's contention that they should also occur on the side wall of the cavity.

An interesting counterpoint to the optimistic accounts of the use of domain decomposition methods was provided by J. Cahouet of Électricité de France, Chatou. He found that in the solution of time-dependent incompressible flows that domain decomposition methods can actually take longer (as much as 10 times longer) than global solutions and only by a judicious combination of finite element and finite difference calculations was domain decomposition computationally competitive. Even with parallel processing, Cahouet maintained that domain decomposition methods possess no computational time advantages. In addition, he said that the advantage of the Cray 2 and its enormous (256 Megabyte) in-core memory eliminated the importance of minimizing in-core storage and thus this characteristic of domain decomposition methods was of little interest. The sole remaining advantage of domain decomposition methods, Cahouet said, was that geometrically complex geometries could be easily treated.

Conclusion

The large attendance at this meeting, as well as the interest shown in the presentations, clearly indicated that domain decomposition methods are currently a very popular computational technique. Although in concept the method is obvious and its advantages easily recognized, the development of an efficient and robust algorithm which takes full advantage of the speed of parallel computation is far from simple. Clearly the most important problem remaining to be solved in conjunction with domain decomposition methods is concerned with the efficient transfer of data between various subdomains. Perhaps this can be solved by means of new computer architectures.

The theoretical and applied presentations at the meeting indicated to me that a firm theoretical basis for domain decomposition has been laid and a wide number of situations exist where the

technique has been profitably employed. Further developments in this area will be reported at the First International Conference on Industrial and Applied Mathematics in La Villette (Paris) in June, and a sequel to the present conference is being planned to take place in approximately 2 years.

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1/13/87

Physics

ONR BRANCH OFFICE LONDON SPONSORS A SESSION ON INTERFACIAL PHENOMENA IN MICRO-ELECTRONICS

by Paul Roman. Dr. Roman is the Liaison Scientist for Physics in Europe and the Middle East for the Office of Naval Research's London Branch Office. He is on assignment until September 1988.

In conjunction with a NATO-ASI course on interfacial phenomena, the European Physical Society organized a Liquid State Conference (as well as a summer school on Physicochemical Hydrodynamics). All meetings were held at La Rabida (near Huelva), Spain; the conference itself took place from 12 through 15 July 1986. At this Liquid State Conference, the London Branch Office of ONR sponsored a special session on Interfacial Phenomena in Microelectronics.

This article reviews the talks presented at the special session.

Theory of Solidification

Professor Dr. H. Müller-Krumbhaar (Research Center, Jülich, West Germany) gave two lectures on the theory of solidification. One was a formal regular lecture on Pattern Formation in Dendritic

Crystallization; the second was a specialized seminar on Dynamic Coarsening of Crystal Surfaces.

The first lecture concerned itself with the formation of instabilities at the growth-front of almost-two-dimensional solidifying layers of materials absorbed on a substrate. This occurs, for example, during liquid phase epitaxy of metallic or semiconducting materials on a substrate, but has a much broader significance in many solidification applications. For the first time, a full treatment of the nonlinear effects at the solid-fluid interface, as well as of the long-range effects of the diffusion field was presented. The calculation confirmed recent speculations which stipulated that the selection of the growth-rate of such a dendritically growing layer can be understood on the basis of the so-called needle crystal solution. In particular, these now exact calculations should allow one to make quantitative predictions for the distribution of the chemical components in the resulting crystalline phase.

Müller-Krumbhaar's second seminar was concerned with the formation of macrosteps on crystal surfaces by coalescence of monatomic surface steps. Even carefully prepared surfaces of substrate material are usually not exactly planar, but look like a staircase with very low slope. A single screw-dislocation is sufficient to cause such (spiraling) steps everywhere on an otherwise perfect surface. Particularly cumbersome for device manufacturing is the fact that, under thermal influence, these steps tend to collide, forming macrosteps of tens or hundreds of atomic heights. This produces a macroscopically rough surface. The speaker gave a quantitative theory for this phenomenon, explaining the relative importance of experimental parameters. The theory is in very good agreement with experiments and computer simulations.

Layered Semiconductor Structures

Dr. K. Ploog (University of Stuttgart, West Germany) presented a detailed study of the growth and properties of layered III-V semiconductor structures used in the field of advanced photonic and electronic devices. These devices require thin layers, abrupt junctions, precise dopant control, and multiple layers. For nearly two decades the technique of molecular beam epitaxy (MBE) has been an excellent choice to provide atomic abruptness and smoothness between layers of different lattice-matched and lattice-mismatched crystalline semiconductors at their interfaces (i.e., at heterojunctions). The abrupt discontinuities in conduction and valence band edge produced by discontinuities in electron af-

finity across the heterojunction can lead to new electronic phenomena due to the reduced dimensionality in the layered material.

Ploog's talk demonstrated the unique capability of MBE to synthesize III-V semiconductors in well-defined geometrical and spatial arrangements. He showed how, based on the shrinkage of the physical size of materials from micrometer to nanometer dimensions, the concept of bandgap (or wavefunction) engineering in quantum wells and superlattices is exploited. Quantum-well heterostructures made of the materials systems $\text{GaAs}/\text{Al}_x\text{Ga}_{1-x}\text{As}$, $\text{Ga}_x\text{Ga}_{1-x}\text{As}/\text{Al}_x\text{In}_{1-x}\text{As}$, and $\text{GaSb}/\text{Al}_x\text{Ga}_{1-x}\text{Sb}$ are important for photonic devices covering the wavelength range $0.65 \mu\text{m} < \lambda < 1.75 \mu\text{m}$ and for high-speed electron devices. New electronic phenomena based on quantum confinement and tunneling of carriers in these multi-quantum-well heterostructures and superlattices have led to the development of novel devices, including quantum-well lasers, bistable optical devices, high-speed optical modulators, new avalanche photodiodes and staircase photomultipliers, high electron mobility transistors, hot electron transistors, etc. These were discussed in connection with some selected examples of the growth, the physics, and the performance of such devices.

In the concluding part of the lecture, Ploog examined the limits to further miniaturization. He emphasized that progress in this direction requires the fabrication and investigation of semiconductor structures that are atomically engineered in all three dimensions to nanometer design rules. Therefore, in the future not only a depth control in the z axis direction but also a control of the lateral size (x, y axis) will have to be developed. This may be achieved by appropriate fine-line lithographic techniques with monolayer resolution.

Crystal Growth Under Microgravity

The third speaker of the special session, Dr. D. Schwabe (University of Gießen, West Germany) expounded a topic which was somewhat distinct from the areas covered by the two other participants, but it fitted more smoothly into the general framework of the larger Europhysics conference. In his talk, entitled Thermocapillary Convection in an Open Cavity under Microgravity, Schwabe reported the very first results of an experiment done during the D1-Spacelab mission in November 1985. The main objective was to observe thermocapillary convection without coupling to buoyant convection.

A rectangular cavity (20×20×20 mm) was constructed by melting paraffin tetracosane in an open cuvette made from quartz glass. The cavity was placed between two heating blocks which served to define the temperature difference ΔT along the free surface. To guarantee a temperature gradient mainly along the free surface, the cavity was surrounded by a double-walled insulation of quartz glass plates. Tracer particles in the melt were used to show stream lines and velocity distribution of the convection in a vertical central light cut. The light cut was observed by a 16-mm camera through the transparent side wall. The main advantage of using a gap (compared to a float zone configuration) is the visibility of the region near the free surface.

Unfortunately, the fluid was not clean enough to avoid buildup of a dirt layer on the free surface, which behaved like a solid skin, suppressing thermocapillary convection totally for small Marangoni numbers (small ΔT). The solid skin ruptured only at high Marangoni numbers ($Ma \sim 5 \times 10^5$); then the main part of the free surface became clean, and strong thermocapillary convection was observed. The velocity along the free surface from hot to cold was 20 mm/sec, and the back flow penetrated deeply into the bulk fluid.

It is regrettable that the speaker did not make sufficiently clear the importance of this experiment on the future space-based technology of microelectronics device fabrication.

Concluding Remarks

I have only sketched the talks that were delivered in the ONRL-supported session. But similar topics were also covered in many other contributions to the conference as a whole and the summer school. The set of abstracts of all the talks has been published by the European Physical Society, under the title *Europhysics Conference Abstract Number 10E*. The editor (as well as the chairman of all activities) was Professor M.G. Velarde, UNED, Madrid, Spain.

It may be worthwhile to note that the larger conference had 130 participants (coming from 21 countries; most of them from Spain, the US, and France, in that order); and the vast majority of these colleagues also partook in the ONRL-sponsored special session.

OPTICAL COMMUNICATION CONFERENCE DRAWS CROWDS TO BARCELONA

by Paul Roman.

The 12th European Conference on Optical Communication (ECOC) took place at Barcelona, Spain, from 21 through 25 September 1986. The host of the conference was "Telefonica," the rapidly growing and respectable Spanish national telecommunication authority. Several Spanish (and Catalan) ministries and scientific societies added support and organizational cooperation, while the official sponsoring agency was the Convention of National Societies of Electrical Engineers of Western Europe (EUREL).

Since the previous ECOC meetings habitually raised basic issues that, within a couple of years, led to technological advances (or became discredited and were forgotten), and since optical communications technology is probably on the verge of major breakthroughs (coherent communication systems, purely photonic devices, monolithic integration, nonlinear effects in optical cables, including soliton propagation), it is surely not surprising that the conference was attended by over 800 people. Even though the crowd was formidable and strained to the limit the adequacy of the modern conference facilities at the Palacio de Congresos, the meeting was smaller than a year ago in Venice, when ECOC was co-joined by the International Conference on Integrated Optics and Optical Fiber Communication (see ESN 40-2:66 [1986]).

There were 108 oral presentations given in 28 sessions (and, alas, 19 poster displays exhibited for a 3-hour period). Twenty-one of the talks were invited papers (30 minutes long) and the rest, the contributed papers, were given 15 minutes each (including discussion). It was necessary to have at all times two parallel sets of sessions. Despite the rapid pace, the meetings were well structured and enjoyable, thanks to the very careful preparatory work of the 22-member preparatory committee which, apparently, requested a standard format from all speakers. (It worked!)

Even though it sounds odd for an "all European" conference, many of us were not surprised to note that the majority of the speakers were Japanese. Speakers came from 12 countries. In particular, there were 35 from Japan, 23 from the UK, 19 from West Germany, 12 from Italy, 12 from the US. (France, this time, had a surprisingly moderate showing, six, which was almost the same as the Spanish presence.)

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For the first time in ECOC's history, presentations in the area of devices and integrated optics dominated the show (44 percent of the talks). Presentations on fibers (40 percent), and systems (16 percent) completed the agenda. Interestingly enough, there were many fewer talks on sensors and detectors than in the past. The talks covered the following topics:

1. Optical fibers: materials, processes, fabrication, measurement, splices (3 sessions)
2. Optical fibers: special properties, including polarization-preserving fibers (4 sessions)
3. Mid- and far-infrared fibers and systems
4. Fiberoptic devices, including fiber sensors (2 sessions)
5. Semiconductor lasers (2 sessions)
6. Integrated optics (2 sessions)
7. Waveguides and nonlinear optics, including switching and optical amplification (4 sessions)
8. Coherent optical systems (3 sessions)
9. Systems-technology, including MUX/DEMUX (4 sessions)
10. Photodiodes and receivers.

In the rest of this article, I shall completely ignore papers on fibers and networks. For reasons of personal interest (and without prejudice as to the importance or quality of the talks) I shall only survey some selected presentations in areas 5, 6, and 7. But for colleagues interested in any other topics, I will be glad to send duplicated copies of selected and specified talks which have been beautifully edited and printed in three volumes (called "Technical Digest," and published by the Telefonica). I also have a list of participants to share.

Advances in Semiconductor Lasers

Distributed feedback (DFB) laser devices had a grand day at this conference: they seem to be the light sources for optical communication.

H.P.M.M. Ambrosius (Philips, Eindhoven, the Netherlands) started off the discussions with a report on the fabrication and performance-study of high-efficiency, low-threshold 1.55- μm DFB buried heterostructure devices with a first-order grating in InP. The grating was produced holographically with an Ar laser. It was possible to achieve about 0.06 mW/ma efficiency for devices coupled into single-mode fibers; at the same time, single longitudinal-mode operation could be maintained. But, probably due to improper cleaving, some double-mode behavior was also observed occasionally.

I. Mito, on behalf of the NEC Corporation, Kawasaki, Japan, gave a closely related talk on highly stable, single-longitudinal-mode DFB laser diodes for 1.5- μm radiation. The distinguishing feature of the NEC devices is that they employ a $\lambda/4$ shift. Stable 30-mW single-longitudinal-mode CW-operation was achieved, even up to 100°C ambient temperatures, and under 4-Gb/s modulation. The threshold current for the experimental devices was around 25 mA, and the slope efficiency 0.17 mW/ma.

F. Favre (Centre National d'Études des Télécommunications (NET), Lannion, France) talked also about quarter-wave-shifted DFB lasers. His talk was more on the basic research side than the above mentioned ones, and he analyzed the effect of weak reflections on the spectral line width of $\lambda/4$ -shifted DFB laser diodes. He clearly demonstrated that such DFB's are considerably less sensitive to external optical feedback than conventional DFB's or Fabry-Perot lasers. They are the most promising candidates for coherent transmission systems, and perhaps the technique can be used also for optical isolators.

S. Yamakoshi presented very interesting novel engineering progress achieved at the Fujitsu Laboratories, Atsugi, Japan. These scientists succeeded for the first time in using chloride vapor phase epitaxy to grow a Fe-doped semi-insulating InP blocking layer (resistivity: $4 \times 10^8 \Omega \text{ cm}$). They developed a completely flat-surface, buried heterostructure laser embedded within this layer; the laser has extremely low capacitance and has practically no roll-off.

M.-C. Amann and colleagues from Siemens, Munich, West Germany, presented a status report of their progress in developing InGaAsP-InP metal-clad ridge-waveguide lasers, a focal topic at Siemens. They have now devices with threshold currents below 19 mA (for $\lambda=1.3 \mu\text{m}$) and 40 mA (for $\lambda=1.55 \mu\text{m}$). Modulation bandwidths of 6 GHz (analogue modulation) and 8 Gb/s (for random pulse modulation) were obtained; dynamic single-mode emission could be maintained up to 4 GHz.

I was quite impressed by the work of H. Olesen at the Telecommunication Research Laboratory, Copenhagen (done in cooperation with the Technical University of Denmark at Lyngby), who constructed a fiber-optic ring laser based on a 880- μm traveling wave amplifier. The light/current characteristics, spectral properties, and intensity-noise spectra have been studied. A detailed theoretical analysis was well confirmed by careful experiments. Perhaps I should note that at the heart of the system there is an optical amplifier made by giving an

antireflection coating to an AlGaAs laser and connecting this into a single-mode coupler.

Integrated Optics

The keynote address was given by S. Sasaki (Central Research Laboratories, Japan), who talked about the next generation of optical communication devices, which will integrate DFB lasers, low-loss waveguides, optical switches, laser diodes, and receiver circuits. The Central Research Laboratories' current frontline work focuses on two topics: (1) DFB lasers integrated with an index-tunable external wave guide and (2) DFB's equipped with an optical switch. The first effort, Sasaki explained, is important because it permits the construction of very-narrow-bandwidth coherent communication sources. In the second area, the Japanese group had considerable success by developing a new solution--viz., creating an index of refraction change by current injection. Sasaki also noted that the same device may also be used for optical amplification, and they already demonstrated 24-dB gain.

The second invited talk, presented by M. Shirasaki on behalf of the Fujitsu Laboratories, was on a rather different area where integrated optics may become crucial: he talked about optical isolators for single-mode fiber communications. This function is achieved by using the Faraday effect, and then it becomes necessary to integrate the polarizer and the Faraday rotator, which are made from different materials. The Fujitsu group devised a high-performance polarizer made of a birefringent rutile wedge. The Faraday rotator, on the other hand, was a disk made of yttrium iron garnet (YIG). The scientists were successful in broadening the wavelength region with high isolation (this was achieved by using a compensator); they also increased the magnitude of the isolation significantly (by constructing a serialized structure).

The difficult area of integrated optical modulators was approached by the work of A.J. Cook (Heriot-Watt University, Edinburgh) and M.J. Wale (Plessey Research Caswell Ltd., UK). They described the first experimental realization of a Ti:LiNbO_3 -based device which combines a polarization-mode converter with a resonant absorption polarizer. Thus, contrary to conventional directional coupler or interferometer types, the rejected signal is *absorbed* within the device. In this way, a rejection (extinction ratio) of 35 dB was achieved. The device operates at 1.3 μm , but it is not particularly sensitive to the wavelength. It has a very low insertion loss, and it shows

useful response over a range of polarization states.

S. Hata (NTT Laboratories, Japan) considered the receiver-end integration problems. He talked about successful monolithic integration of a Schottky photodiode and a MESFET, constructed in an InAlAs-InGaAs heterostructure.

O. Wada (Fujitsu Ltd., Atsugi) tackled the problem of integrating on one chip several transmitters and receivers, using a set of channels. In fact, he described the successful construction of a single sample (so far) that is the first example of a four-channel AlGaAs-GaAs optoelectronic integrated circuit transmitter-receiver array. The central piece of the chip is, of course, a high-speed optoelectronic switch circuit.

Optical coupling and optical interconnections were considered in two interesting communications.

A Yokohama National University-Tokyo Institute of Technology cooperative research group (represented by K. Kokobun) reported on the uncoupled stacking of parallel antiresonant reflecting optical waveguides (ARROW's), to be used for three-dimensional optical wiring. They succeeded in reducing the loss to 0.3 dB/cm in a wide spectral range. Two ARROW's could be stacked without any coupling even if the spacing was only 2 μm . The trick was achieved by using a $\text{TiO}_2/\text{SiO}_2$ interface reflector.

A somewhat related talk, presented by W.H. Wu, described a JET Propulsion Laboratory-University of California at San Diego effort, leading to the construction of a test chip which incorporated a CMOS-compatible optical gate suitable for microcircuit interconnection. The gate can be addressed by light input from optical fibers or from free space. The risetime was only 34 ns.

Nonlinear Optics

The lively introductory invited talk in this area was given by T.H. Wood (AT&T Bell Laboratories, Holmdel, New Jersey). He first reviewed earlier work on the use of LiNbO_3 (based on the electro-optic index of refraction effect) and on III-V compounds (using the electroabsorptive effect) for various optical communication devices. Then he pointed out that, with the advent of multi-quantum-well (MQW) structures, a new technology for optoelectronics has developed. This is so because MQW's have an electroabsorption effect 30-60 times larger than conventional semiconductors. Moreover, they are compatible with existing source and detector material systems. Compact and high-speed devices can be easily achieved. As an example, Wood described a

bidirectional optical fiber data transmission system which transmits data at 50 Mb/sec and 600 Mb/sec in the two directions, respectively, over a single-mode fiber, and it does not require an optical source (laser) at the remote location.

Most subsequent talks in the strict area of nonlinear optics in optical communication were, to me at least, of limited interest. However, I want to draw attention to two papers on an interesting use of nonlinear effects in optical waveguide structures: namely, second harmonic generation. This is a promising way to achieve relatively high conversion efficiencies even with low-power sources.

The first talk, read by T. Taniuchi (Matsushita Electric Industrial Co., Ltd., Osaka, Japan) described second harmonic generation with a conversion efficiency in excess of 1 percent in a proton-exchanged LiNbO₃ optical waveguide. The GaAs driving laser diode supplied 20-mW fundamental frequency power at 0.84 μ m. The mechanism of the process is based on Cerenkov radiation, and the second harmonic is emitted into the substrate at the Cerenkov angle. An interesting technical point is that, for the proton exchange phosphoric acid (rather than the conventional benzoic acid) was used as the H⁺ source.

In a related talk R. Regener and W. Sohler (University of Paderborn, West Germany) reported on the efficient second harmonic generation in a Ti:LiNbO₃ matched waveguide resonator. Their trick was the use of asymmetrical, matched resonators, which led to complete power coupling (i.e., zero reflectivity in resonance), and thus, to a strong enhancement of the fundamental field. The power source was a 1.09- μ m Ar ion laser. With only 100- μ W input power, a second harmonic power of 100 nW was achieved (i.e., a conversion rate of 1 percent/mW, if one can extrapolate).

Also in the area of nonlinear optics were a few talks on optical amplification. I mention two.

In an invited review talk J.C. Simon (CNET, Lannion, France) gave a scholarly summary of the state of the art. In the concluding remarks, he emphasized that optical amplification has already been demonstrated successfully by using semiconductor laser amplifiers. Further improvements are expected from nonlinear-optics-based fiber amplifiers (Raman and Brillouin devices). He expressed his optimistic view regarding the future use of the bistable operation of Fabry-Perot or DFB diode laser amplifiers for optical processing and for digital optical computing—but, unfortunately, he did not provide convincing arguments.

I was impressed by a presentation of G. Groszkopf and his colleagues from the H. Hertz Institute for Communication Technology, Berlin, West Germany, in which experiments were reported where two channels are simultaneously amplified. The amplifier was based on a Fabry-Perot resonator, equipped with a very high-quality antireflection coating. The cross-talk was carefully studied and the scientists concluded that it is connected with two effects: a shift of the residual Fabry-Perot resonances, and a lowering of the gain-curve due to the passage of the second channel signal through the amplifier.

Optical Switching

Topics in this area are of course highly multidisciplinary, and so perhaps it is best to discuss them under one heading, even though some of the work fits in waveguide research, some into nonlinear optics and bistability, some into integrated systems.

The keynote address was given by J.D. Midwinter (University College, London, UK) who surveyed the area of optically activated optical switching. He described several possible paths to what he prefers to call "digital optics" rather than the more restrictive and also probably overoptimistic term "optical computing" (see ESN 39-10:480-483 [1985]). In his view, the current realities necessitate a hybrid optoelectronic approach. One of the specific topics he described in some detail was his current successful research on constructing a synchronously clocked switching matrix, in which the first step is the building of logical exchange-bypass submodules. Given these, a particularly simple and elegant optical implementation suitable for integration into a switching matrix can be based on the "perfect shuffle" principle. Midwinter's research-model sample takes full advantage of the zero time-skew properties of free-space optics and leads to the possibility of very compact parallel pipeline processor architectures that have all processor logic contained in a few planar optical logic arrays. He concluded, rather convincingly, by saying that within 5 years it may be possible to demonstrate many of the key subsystems needed for an optically activated packet or circuit cross-point switch, handling data at rates up to 10 Gb/sec per fiber, and perhaps servicing 128 or more such fiber highways.

In a second invited talk J.F. Huignard (Thomson-CSF, Orsay, France) addressed a more specific aspect of optical switching. He described ways to construct a two-dimensional optical switch which exploits the parallel space transmission

capabilities of free-space optical beams. The crux of the matter is the arrangement for fast and accurate angular deflection of the beam emerging from the array of input fibers. One special method advocated by Huignard was the use of advanced holographic methods. He described several experiments on the construction of dynamic holographic devices.

A collaboration between the Fondazione V. Bordini (Rome, Italy) and the Optical Sciences Center (University of Arizona, Tucson, Arizona) devoted work on all-optical switching through nonlinear stationary wave instability in a nonlinear coherent coupler. The talk was presented by S. Wabnitz (Rome). The described research consisted of a theoretical study of spatial instabilities for stationary nonlinear waves propagating in two coupled parallel thin-film waveguides with homogeneous positive or negative nonlinearity. For me, the noteworthy point of this talk was that it was the only one concerned with nonlinear waveguides.

H. Fouckhardt (University of Braunschweig, West Germany) reported on a new nonlinear effect that the scientists at the Institute for High Frequency Technology discovered and which, they hope, may be used for all-optical switching and modulation. The effect occurs in GaAlAs strip waveguides embedded in unbiased p-n junctions. The scientists found a distinct nonlinearity in intensity transmission at submilliwatt power levels. This is due to the Franz-Keldysh effect which is self-induced by the transmitted light.

Finally, I want to give credit to T. Hermes (H. Hertz Institute, Berlin, West Germany) who, in a beautifully designed invited talk, gave not only an overview but also a critical evaluation of the state-of-art and future aspects of optical routing. The talk focused on space division multiplex switching based on LiNbO_3 technology. Basic switches, as well as many proposed architectures, were carefully explained. I think that the conclusion of the analysis, although not a happy one, is rather important: high-speed, large-scale routing systems cannot be based on LiNbO_3 switching matrices. More generally: Hermes believes that the foreseeable future of optical routing will lie in the field of special applications related to small local area networks.

Concluding Comments

To my surprise, despite its large size, the ECOC 86 was a success. The international organization committee and the program committee deserve maximal credit for this.

As I mentioned in the introduction, the meeting was dominated by the Japanese--but I am a bit worried about the nature of their approach: I saw much more "clever" engineering than basic research orientation on their part. Is this a bad omen for the future? Or are we prejudiced for believing so firmly in the necessity of broad-based basic research as a prerequisite for high-tech?

Related to this observation is my surprise in registering that there was no Soviet or Eastern European contribution to the proceedings. Has this fact merely a political cause or is there here, too, a science-development-lesson to be learned?

The next ECOC is already "in the works": it will be held at Helsinki, Finland, 13 through 17 September 1987. Interested colleagues should write to: ECOC 87, c/o Sähköinsinööri, Merikasarinkatu 7J53, 00160 Helsinki, Finland.

2/24/87

Space Sciences

NATO ADVANCED STUDY INSTITUTE--PHYSICAL PROCESSES IN THE INTERSTELLAR MEDIUM

by Philip R. Schwartz. Dr. Schwartz is a member of the Space Science Division, Naval Research Laboratory, Washington, DC.

Introduction

The NATO Advanced Study Institute--Physical Processes in the Interstellar Medium--held at the Irsee Conference Center near Kaufburen, West Germany, was an opportunity for senior researchers and advanced students in this field to meet and share ideas and current results. The meeting was hosted by the Max-Planck Institut für Extraterrestrische Physik, Garching (near Munich).

Astrophysicists' ideas of the interstellar medium have changed radically in the past 10 years. This change has been the result of millimeter-wave molecular line observations and data from satellite observatories in the ultraviolet, x-ray and, recently, infrared part of the spectrum. In the old view, the interstellar medium consisted of warm (100 K) clouds of neutral H atoms immersed in a hotter,

more tenuous gas. Molecular line observations added to this view large, dense ($n \geq 10^2 \text{ cm}^{-3}$) molecular clouds consisting of H_2 at lower temperatures (20 to 40 K). New observations are beginning to show that the interstellar medium is even more complex, having a broad spectrum of cloud sizes, densities, and compositions. Although the interstellar medium is intrinsically fascinating, the major question in galactic astrophysics is how these clouds collapse to form stars. Current observations and theory do not come together to form a convincing picture of this process. Most of the topics discussed at the advanced study institute were viewed in the context of their role in star formation or in processes related to star formation. The topics included the structure and distribution of molecular clouds; cloud cores and nearby clouds; triggered star formation; chemistry, dust, and dust formation; and magnetic fields.

Structure and Distribution of Molecular Clouds

Several contributors, including B. Elmegreen (IBM Research Center) and L. Blitz (University of Maryland), reviewed the status of knowledge concerning molecular clouds. In the current view, the interstellar medium is organized into giant clouds containing 10^6 to $10^7 M_\odot$ which inhabit the galactic disk. These clouds are actually complexes of smaller clouds which, in turn, are further fragmented. The fraction of the mass of the interstellar medium in molecular clouds is the subject of some controversy because of uncertainties in the conversion from CO--the molecule actually observed--to H_2 densities. In most of the galactic disk, the atomic and molecular gases appear to have comparable surface density. This uncertainty also means that the gravitational stability of clouds is the subject of debate. It appears as if most clouds are at the edge of stability, but the large complexes are not bound.

In our galaxy, the spiral structure is not clearly evident in molecular material although good evidence for parts of arms does exist. The predominant feature appears to be a ring of enhanced cloud population near a radius of 5 kpc. In other galaxies, notably M31, spiral arms are much more clearly evident in CO observations. This effect may be related to the contrast between arm and interarm populations. Since spiral arms are outlined in young hot stars and are probably the result of gravitational density waves, this mechanism may be a major factor in star formation. B. Elmegreen argued, however, that the role of spiral density waves is more to "orchestrate"

star formation than to trigger individual cloud collapse.

A very important concept which was emphasized by everyone connected with observations was that the interstellar medium has structure on many size scales. E. Falgarone and others noted that, when observed in isotopic CO lines, clouds are not smooth but, rather, consist of clumps and condensations including ones smaller than the telescope beams. She noted that clouds up to masses of $10^4 M_\odot$ are not centrally condensed nor do they show evidence for global collapse. The efficiency of star formation from a fragmented interstellar medium is not, usually, very large. The pressure stability of these clumps against gravitational collapse is not obvious so that some other force such as magnetic pressure or, perhaps, turbulence must support small clouds (otherwise, the star formation efficiency would be unity). However, L.G. Stenholm (University of Stockholm, Sweden) asserted that actual clumps contain only a small portion (<10 percent) of the mass of a cloud. He noted that turbulence theory predicts the behavior of the linewidths and sizes of cloud fragments seen by observers. Comparison of numerical models with observations leads to estimates of the important properties of the interstellar medium, including correlation length, and predicts some of the observed structures including bars and disks.

Cloud Cores and Nearby Clouds

The smallest clumps are often referred to as "cores." They may be associated with the formation of solar-type stars. G. Fuller and P. Myers (Center for Astrophysics and Space Sciences, University of California, San Diego) summarized the properties of some of these cores in the nearby dark clouds in Tau. Typical cores are 0.1 pc in diameter ($1 \text{ pc} = 3.1 \times 10^{18} \text{ cm}$) and consist of 10 to $100 M_\odot$. These objects are very cold and have very small internal motions. The widths of some molecular lines are almost thermal. Many cores have associated young T Tau stars. G. Fuller and P. Schwartz (Naval Research Laboratory, Washington) reported on independent surveys which indicate that about 1/3 to 1/2 of the stars embedded in or near cores have significant stellar winds and, thus, excite flows and turbulence in molecular clouds.

Blitz also discussed some work on very nearby clouds. In his example, dark cloud objects at high galactic latitudes were observed. He found a significant population of small clouds within 100 pc of the sun. Their average properties are similar to other clouds, but they are not the building blocks of giant clouds. Their lifetimes against disruption or

evaporation are quite short. Being nearer, they can be studied in more detail. He finds them to be young ($<10^6$ years), not gravitationally or pressure bound but with supersonic linewidths. These molecular clouds are different from but blend into the galactic HI (atomic gas).

Triggered Star Formation

Since clouds do not appear to be in collapse (held up by some unknown force!), triggering of star formation does not seem necessary but, as several contributors pointed out, there is ample evidence for such triggering. Triggered or sequential star formation accounts for the observation that stars, particularly early types, form in clusters. An equally good explanation for this phenomenon is the fragmentation and collapse of a localized molecular cloud. D. MacCray (Joint Institute for Laboratory Astrophysics, University of Colorado, Boulder) reviewed evidence for supernova-induced star formation in our galaxy and other galaxies in the form of shells and supershells of gas. He presented a theory of multiple supernova explosions in a cluster to form a supershell. Schwartz showed far-infrared evidence for both shell formation and the formation of secondary stars on shells in the other galaxy. He claimed that a significant proportion of the early type stars in the other galaxy is formed in shells.

F. Bertoldi (University of California, Berkeley) presented a different triggering mechanism which might operate on single clumps. He showed model calculations of the effect of photoevaporation on partially ionized globules which indicated that internal focusing of shocks can compress the centers of globules to form stars.

Chemistry, Dust, and Dust Formation

The subject of gas phase chemistry of the interstellar medium and the formation of molecules was reviewed by E.F. Van Dishoeck and A. Dalgarno (Harvard University, Cambridge, Massachusetts). Both talks focused upon the formation of H_2 and CO and how well gas phase reaction schemes predict their ratio. In general these models seem to work very well although a few important molecules seem to be missing. The best example is H_3^+ which should be about an order of magnitude more abundant than current observational limits. Another problem is that the abundance of C inside clouds is too high. It should be primarily found at cloud edges. In general, most of the chemistry would give better agreement with observations if $(C)/(O) > 1$ but, at least in the solar system $(C)/(O) < 1$.

Interstellar dust is both the vital link between stellar energy sources and the interstellar medium, and a possible player is interstellar chemistry. E. Sedlmayr and H.P. Gail (University of Heidelberg, West Germany) showed that dust grains can form in the outflows of late-type stars. Grain nucleation occurs at radii of about $5R_*$ and temperatures below 1000 K. The process results in the formation of small grain nuclei. In carbon stars, chemical pathway analysis leads to the formation of polycyclic aromatic hydrocarbons (PAH's). PAH's are really neither a grain nor a molecule. In oxygen-rich stars, grain formation goes via molecules such as MgS and SiO, leading to the formation of silicate core grains. Both of these types of grains are seen in the interstellar medium. The silicate core grains grow ice mantles and are the large grains responsible for long-wavelength infrared emission while the PAH's are the small, hot grains in the infrared cirrus and in reflection nebulae.

D.A. Williams (University of Manchester Institute of Science and Technology [UMIST], UK) discussed the role of grains in molecule formation. He pointed out that there is no gas phase reaction sufficient to form the H_2 in the interstellar medium. H_2 must be formed on grains. Amorphous silicate grains have massive surface defects providing OH sites for H_2 and other molecule formation. Collisions with atoms and molecules provide many mobile fragments to eventually find defect sites. There is evidence for both H_2O and NH_3 ices which may have formed by this process. H addition can then lead to the formation of CH_3OH and CH_2O (these molecules are all very abundant in dense molecular clouds). If SH^- sites also exist, then molecules like CS, HCS, and H_2CS can form. He pointed out that a major problem is that if a mantle growth-limiting process does not exist, then all molecules will wind up stuck to grains in 10^5 to 10^6 years. Possible mantle-limiting processes include grain-grain collisions, cosmic ray heating and, most likely, star formation. Heating grains to >100 K will evaporate mantles, injecting molecules into the gas.

L. Allamandola and J.M. Greenberg (NASA, Ames Research Center) reviewed the status of laboratory experiments and observations of grain properties. Solid CO is detected in the spectra of about 1/2 of all protostellar objects. Evidence for solid molecules in grain mantles is found in many objects. Band emission which can be identified with PAH's is also found, although whether to call this material a molecule or a grain is

debatable. Greenberg sketched a global picture of grain evolution involving the following steps:

1. Origin of refractory grains in M (and C) stars
2. Molecular cloud phase with accretion and photoprocessing
3. Ejection to diffuse clouds with erosion of volatiles and other photoprocessing
4. Destruction by inclusion in star formation.

An individual grain core can cycle between steps 2 and 3 many times before going to 4.

Shocks are another important factor in both molecule and grain processes. The temperatures and densities of observed interstellar shocks are ideal for the formation of some species. The cooling of shocks by line emission is an important astrophysical problem because it is via H_2 lines. This is the observers' best method of directly observing the most abundant interstellar molecule.

Magnetic Fields

The important area of magnetic fields and their influence in star formation is a controversial topic because interstellar fields are difficult to observe. Essentially three methods of measuring interstellar fields exist: polarization of starlight (by magnetically aligned grains), Faraday rotation, and Zeeman splitting. Polarization is an indirect method since the grain alignment mechanism is unknown. Faraday rotation must be combined with a dispersion measure to measure B so that only lines of sight to pulsars can be used. This means that Zeeman splitting is the most useful approach, but the g factors of most interstellar atoms and molecules are such that the splittings are very small. Only HI and OH are useful. C. Heiles (University of California, Berkeley) reviewed the measurements and showed that the typical average field strengths in our galaxy are $B = 4$ to $9 \mu G$. Zeeman splitting measurements have been made in 100 to 200 places. In HI clouds the usual values are $B \leq 7 \mu G$, in dark clouds typical values are $< 30 \mu G$. The largest values have been seen in a few unusual HII regions like S106 and S88 where $B = 70$ to $120 \mu G$.

The importance of a magnetic field in star formation processes is championed by T. Mouschovias (University of Illinois, Urbana). In his view, the interstellar field is the major factor in "resolving the angular momentum problem." This means that fields couple the angular momentum (of galactic rotation) out of collapsing clouds so that gravity can

overwhelm magnetic pressure. This magnetic braking of clouds is very fast and, essentially, is an Alphen wave coupling between clumps in a cloud. Ambipolar diffusion acts more slowly to dissipate the compressed fields but is rapid enough that reaction back onto an individual cloud is small. Mouschovias showed model calculations which indicated that this mechanism works in simple cases and that, in the general case, the time scales for magnetic braking and ambipolar diffusion are correct.

Conclusions

To a working astrophysicist like myself, the advanced study institute was rather unsatisfying for several reasons. A genuine gap between theory and observation appears to exist in most areas related to the interstellar medium. No good explanation of how molecular clouds are formed or stirred up once they are formed seems to exist. Most of the models rely upon either large magnetic fields or do not reproduce the observed spectrum of sizes. It is also not certain how or why clouds are so fragmented but still appear to be organized in giant complexes. The star formation process itself is not obvious although both stochastic formation and triggered formation probably occur. Once gravitational collapse begins, observational evidence points to a rather orderly evolution to a normal star along sequences which can be analysed and about which good predictions can be made.

The role of dust in both the thermodynamics of the interstellar medium and in molecular formation is still very controversial. In my opinion, at least, grain chemistry probably holds the key to interstellar chemistry.

Meetings like the advanced study institute appear to be more useful than general astronomical gatherings. They focus attention on a limited topic and bring the current experts and the next generation of experts together.

12/2/86

News and Notes

NEW JOURNAL IN PSYCHOLOGY AND EDUCATION

The *European Journal of Psychology of Education*, launched in April, 1986, publishes original contributions in educational psychology. Empirical research,

theoretical and methodological articles, and critical reviews of the literature are welcomed. In addition, two or three book reviews are published each issue, along with reports of major educational conferences. Articles are published in English or French, with summaries in the second language. According to the prospectus, the main aim of the journal is "to contribute towards the creation and development of international contact and towards the development of new links necessary for scientific progress in the Psychology of Education." Editor is M. Gilly, of the University of Provence, Aix en Provence, France. For the 1986 volume, the individual subscription price was \$25 (\$40 for institutions). The journal is published four times per year, for a total of approximately 400 pages.

The first issues look very promising, containing much original research, description of Italy's CNR, a review of the first conference of the European Association for Research on Learning and Instruction (which ONR was instrumental in developing), etc. The language split on the first two issues was approximately 50-50. Educational psychologists with an international bent will profit from this journal. More information, subscriptions, etc., may be obtained from EJPE/ISPA-CRL, Rua Jardim do Tabaco 44, 1100 Lisbon, Portugal.

William D. Crano
2/23/87

THE SECOND INTERNATIONAL CONFERENCE ON PRACTICAL ASPECTS OF MEMORY

The Second International Conference on Practical Aspects of Memory, sponsored by the Welsh Branch of the British Psychological Society, will be held at University College, Swansea, Wales, from 2 through 8 August. Special paper sessions will be focused on neurological memory disorders, autobiographical memory, face memory, children's memory, memory for action events, aging, ecological memory, eye-witness memory, prospective memory, dyslexia, memory aids, and the effects of stress and ill-health on memory. For information, registration forms, etc., write to Michael M. Gruenberg, University of Wales, Department of Psychology, University College of Swansea, Singleton Park, Swansea SA2 8PP Wales. Telephone: 0792 205678.

William D. Crano
2/23/87

FUNGUS PROVIDES ECONOMICAL "FILTER" FOR INDUSTRIAL EFFLUENTS

An unwashed coffee cup left standing in her laboratory provided the final answer to Professor Margalith Galun's lengthy research. A professor at Israel's Tel Aviv University, she had been seeking the right fungus to "filter" heavy metal from industrial waste water, and on seeing the film of fungus growing on the coffee residue, decided to experiment with it--and eventually found the fungus that is the key to a new process.

The process removes heavy metal contaminants (including mercury, uranium, lead, zinc, cadmium, nickel, silver, copper, and chromium) from industrial effluents, and allows the continuous reuse of the water involved. Contaminated water, instead of polluting rivers and streams, can thus be cleaned up and recycled. Among the industries in which the new method may be used are mining, chemicals, metal processing, and electroplating.

Many microorganisms are able to absorb metals from aqueous solutions. But the fungus used in Galun's method is much more efficient than the others because it has a higher absorptive capacity. It is also more economical: this particular species can be cultured on waste products from the food and beverage industry.

The absorption process is fast--it does not require long contact between the fungal mass and the effluent. The mass can be stored between production and use, and its absorptive capacity does not deteriorate in cool storage. The metal elements can be easily removed from the fungal mass and the fungus reused. This procedure can be repeated several times.

Galun's method has been shown to work well in the laboratory. Ramot, the University Authority for Applied Research and Industrial Development Ltd., will market the industrial upscale of the process.

For further information, contact Mr. Zvi Shoshan at Ramot, 32 University Street, Ramat Aviv. Telephone: 03-420113, or 03-428765.

C.J. Fox
2/24/87

A PASSIVE PREPROGRAMMED MEMORY USING THICK-FILM TECHNOLOGY

Introduction

Welwyn MicroCircuits has been a major influence in hybrid circuits for 25 years, and today is Europe's largest

independent custom hybrid house. The company comprises four separate divisions of Crystalate Electronics Ltd. (the parent organization)--Welwyn Printed Circuits, Welwyn Networks, Welwyn Volume Hybrids, and Welwyn Advanced Products--and employs over 500 people at the Bedlington, Northumberland site. I was invited to visit Welwyn by one of the pioneers in thick-film technology, Dr. Peter Kirby OBE, who is Group Director of Research for Crystalate Electronics and also a Visiting Industrial Professor at the University of Edinburgh. Kirby had told me a year earlier not to waste all of my time in the southeast of England when the good hybrid work is going on in the north, and I did find some very innovative research at Welwyn.

A Thick-Film Memory

Standard thick-film materials and processing equipment are used to build a relatively simple form of two-level multilayer thick-film circuit. The device so produced provides a particular type of memory whose characteristic is to store in a highly reliable and nonvolatile form a single and unique member of a sequential series of numbers or characters. This type of device forms a key feature in the field of electronic identification--a subject of rapidly growing importance in many different areas of application.

Both conductor levels are processed using Pd/Ag thick-film inks, and the intervening insulator is provided by a thick-film dielectric. The code, which is unique to each device, is achieved by using a particular pattern of interconnecting links formed by vias between the conductors, as shown in Figure 1. A relatively novel step is the manner by which the required pattern of vias is produced in the dielectric, exposing the underlying fired conductor at selected points to which contact is made later when the top layer of conductor material is deposited. Because each individual unit requires a unique pattern of interconnecting vias through the dielectric, it was decided to use a programmed laser. Work indicated that the YAG lasers used for trimming thick-film resistors could be readily adapted for opening small holes in the dielectric. An innovative feature was the use of a pigmented dielectric which readily absorbs the energy from the laser beam. The underlying Pd/Ag conductor reflects the laser radiation when the hole has been formed, which makes the production of good vias relatively insensitive to variations in the laser parameters. It was found that clean hole in the dielectric could be produced with diameters of about 25 μm , which is smaller than

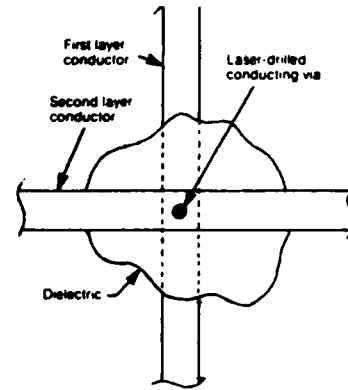


Figure 1. One element of the thick-film memory.

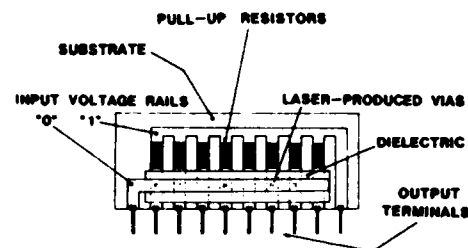


Figure 2. A single row bit set programmed for the code work 00101001.

desired for this application where the conductor track is not likely to be less than 250 μm wide. Consequently, they produce a series of holes in a scatter pattern in the region of each crossover area.

Several different circuit arrangements can be used to provide memory devices. One of the most simple is a single bit set, as shown in Figure 2. The underlying conductor is a number of separate output terminals, each of which may be attached through a "pull-up" resistor to a common voltage bus. As relatively wide tolerances in the resistors are permissible, printed and fired thick-film resistors without additional trimming provide an ideal and economic solution. The tracks near the terminals are then coated with a dielectric layer, and interconnecting vias are produced by the laser to selected output tracks according to the required code. This is followed by the deposition of one single input conductor providing the other voltage bus. The output terminals will then carry one of the two possible input levels, thereby representing the numerical code. The output can be read in a serial or a parallel mode according to the type of decoding circuit used. The number of

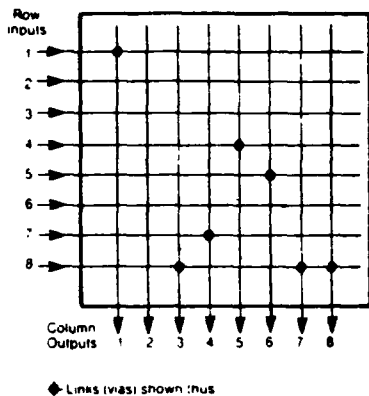


Figure 3. An array programed for the 8-bit code word 10,874,588.

alternative combinations for this device is 2^n , where "n" is the number of output terminals.

A two-layer matrix, shown schematically in Figure 3, provides capacity for storing a much larger number of separate codes, but the decoding circuitry becomes somewhat more complex. The number of combinations for this device is N^m where "N" is the number of inputs and "m" is the number of outputs. The 8x8 array of Figure 3 can store any one of more than 10^7 different 8-bit code words. Welwyn has built matrices as large as 16×16 , which can hold any one of more than 10^{19} different 16-bit code words.

These preprogramed memories can be built as discrete units on standard chip carriers for surface mounting. An alternative and much more attractive packaging scheme is to produce the device on one section of substrate and use the rest of the substrate to accommodate the electronic interrogating system. The resulting hybrid circuit is small, rugged, and economical.

Summary

The thick-film preprogramed memory for electronic recognition and identification systems developed at Welwyn Micro-Circuits is the most nonvolatile memory I can imagine. It is totally unaffected by magnetic fields, any wavelength or type of radiation, temperature (at least to 500°C), or any other environmental influence I can think of short of direct impact by a projectile. Such ruggedness plus the low cost should make this memory attractive for a number of applications.

Robert W. Vest
2/23/87

METAL SURFACE TREATMENT, STUDIED AT CENTRE DE RECHERCHES D'UNIEUX IN FRANCE

USINOR, the very large metallurgical industrial group in France, has research and development laboratories at three different locations. Welding, refractories, and tin plating are studied mainly in the laboratory in Dunkerque; automobile metal sheeting, adhesion problems, stamping, and atmospheric corrosion are investigated in Montataire; surface treatments and corrosion are the main studies at the Centre de Recherches d'Unieux (UNIREC), a subsidiary of USINOR, in Firminy. The industrial laboratories at UNIREC were previously the research center of Creusot-Loire and were taken over by USINOR about 4 years ago.

The surface treatment department at UNIREC is relatively small, consisting of five engineers with 15 technicians. The manager of the surface treatment department is R. Levêque; ion implantation and laser studies are carried out by C. Chabrol and M. Robelet, chemical vapor deposition (CVD) by J.F. Nowack, and plasma deposition by A. Boucher. Despite the small number of staff, they have been able to accomplish extensive and useful developments through cooperative studies with the École des Mines de Nancy, Institut de Physique Nucléaire (IPN) Villeurbanne, Lyon, and the Laboratoire de Metallurgie Physique, Université de Poitiers.

UNIREC has available a wide range of techniques, and its staff is studying many processes. The techniques include:

1. Ion implantation (nitrogen). An implanter is available at IPN with variable voltage to 150 kV, vacuum of 5×10^{-6} torr, liquid nitrogen traps to avoid contamination by hydrocarbons, and water-cooling of the target. A semi-industrial implanter is also available at UNIREC. Use of the two implantation systems has been compared; the degree of pollution by carbon and oxygen is higher when using the industrial unit to implant, yet good corrosion resistance of stainless steel is obtained, even better than when using the IPN system. This appears to be due to a reduction in Cr from the surface of the stainless steel when using the cleaner IPN system, whereas the Cr reduction does not occur when using the industrial system with its slightly higher degree of carbon and oxygen pollution (Fayeulle et al., 1985).

2. Chemical vapor deposition (CVD). There are systems for conventional thermal CVD, plasma-assisted CVD (PACVD), and organometallic CVD (MO-CVD) for depositing coatings such as Ti, Cr, V carbides or nitrides. The pilot system can accept

specimens up to a maximum capacity of 1 m in length, 0.35 m in diameter, and 300 kg in weight.

3. Laser treatments. The equipment used is located elsewhere in France:

- A 5-kW CO₂ laser at Etablissement Technique Central de l'Armement (ETCA), Arcueil, Paris
- An excimer laser at Compagnie Industrielle des Lasers, Institut Nationale des Science Appliqué, Lyon. Transformation hardening, surface alloying, cladding, and amorphization studies have been carried out.

4. Plasma-transferred arc hardfacing. Coatings of nickel-base, cobalt-base, iron-base alloys are produced in the installation whose maximum capacity is 3 m in length, 0.08 m in inner diameter, 0.6 m in outer diameter and 700 kg in weight.

5. Sputtering and ion implantation systems are being combined in order to carry out ion-beam-enhanced deposition (IBED).

The properties UNIREC has addressed include those associated with tribology of friction and wear problems (cold and hot forming) as well as wear problems in corrosive environments. To solve these problems, surface treatments are carried out at the lowest possible temperatures.

The research group at UNIREC has been able not only to carry out basic studies on the mechanism of wear resistance improvement by ion implantation but also to carry the results through to the marketing of improved products (using the tradename IMPLANTEC). Wear-resistant improvement by N implantation has been obtained for steel, WC, and Ti alloys (Robelet et al. 1984b, Fayeulle et al. 1984, 1985 and Moncoffre et al. 1985). Following are some special aspects of this development work:

1. The profile of the implanted nitrogen is determined by Nuclear Reaction Analysis (NRA) using the nuclear reaction $^{15}\text{N}(\text{p}, \alpha, \gamma)^{12}\text{C}$ (Robelet et al., 1984a; Fayeulle et al., 1985). This nondestructive method has a resolution of 5 nm in steels and 9 nm in WC. For industrial use, the method of Glow Discharge Optical Spectroscopy (GDOS) has been developed at UNIREC, and when compared to NRA it demonstrated very good agreement (Hocquaux and Leveque, 1984). The GDOS analyses are much simpler to carry out than NRA. It has permitted detailed studies to be carried out in an industrial environment to characterize and optimize the effects of implantation energy, ion fluence, ion beam current density, temperature of the specimen,

and vacuum conditions (Robelet et al., 1984b).

2. The nitrogen-profile in sintered WC has been determined for different degrees of surface wear. The nitrogen profile, after bombardment by 10^{17} N ions/cm² at 40 keV, is initially within 100 nm of the surface, but persists to 400 nm after wear (Robelet et al., 1984b). The migration of the nitrogen under wear is not fully understood.

3. The surface layer of nitrogen-implanted steels has been studied by Mössbauer and Nuclear Reaction Spectroscopy and by electron microscopy when the hardening process can be related to the precipitate of fine particles of very hard nitrides and carbonitrides (Moncoffre et al., 1985). The surface nitriding of Fe causes the surface to be under compression due to the insertion of the nitrogen atoms and to the formation of $\gamma\text{Fe}_4\text{N}$ and $\epsilon\text{Fe}_{2.3}\text{N}$ (Leveque et al., to be published).

Other Activities

The research center at UNIREC covers many other activities, and there are several other laboratory groups. Three areas of research of particular interest are:

1. Composites. UNIREC has a general laboratory concerned with a range of composite structures. One composite study of interest concerns the reinforcement of cement using scrap metal cuttings. Although some preliminary results have been obtained, this study needs careful consideration of the nature of the cement being used and of the treatment of the metal cuttings. However, earlier studies of this in other laboratories have not produced useful results.

Other composites are based on reinforced plastics, and still others use lightweight aluminum alloys--where some progress has been made in replacing steel armor under special conditions.

2. Corrosion. Two categories of corrosion problems are treated: the first one relates to the nuclear industry, the second relates to the chemical and petrochemical industries.

Electrochemical experiments are conducted in autoclaves at high temperatures (up to about 360°C) and high pressures and in some cases with mechanical loads. The applied load in the autoclave can be constant load testing, constant extension rate or under friction. The latter uses a system modified at UNIREC permitting fatigue testing under cyclic conditions of compression-tension with applied torsions. Corrosive solutions investigated include chlorides, mineral acids, H₂S-containing media and organic acids. Studies have been carried out on steels of

stress corrosion cracking, pitting, and crevices, and hydrogen embrittlement has been studied on samples of steels.

Conclusion

The research center of UNIREC is a well-balanced industrial development unit. With relatively modest equipment but working closely with university laboratories, they have been able to carry out some very useful developments, investigating the mechanism and processes involved, while also converting laboratory results into industrial applications.

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Louis Cartz
10/30/86

UK HEATS UP GALLIUM ARSENIDE FIRES

In January the UK's Minister for Information Technology, Geoffrey Pattie, announced support of up to \$38 million for UK users and manufacturers of gallium arsenide integrated circuits. (See ONRL report R-7-86 for background.) In his announcement, Pattie said, "Gallium arsenide could be the next generation of microelectronics chips. Because of special properties this could mean faster computers, microwave systems, and cheaper direct broadcasting by satellite systems."

The support is aimed to speed up industrial exploitation of the UK research in gallium arsenide and lead as soon as possible to marketable products. The true intent in Mr. Pattie's words, is "to assist in addressing the increasing competition from Japan and the US."

The initiative, intended also to reduce fragmentation and duplication of effort by UK industry, invites proposals, and these will be judged on their compatibility with the UK industry strategy, their technical merits, the degree of collaboration, and the overall benefits to the UK. Significantly (in the context of the recognized need for a sufficiently large research/industrial base) collaboration with other European companies will also be taken into account in the judging.

C.J. Fox
2/17/87

COMBUSTION AND ENERGY STUDIES AT THE UNIVERSITY OF LEEDS

Introduction

The Center for Combustion and Energy Studies at the University of Leeds was founded in 1967 by Professor P. Grey, of the Department of Physical Chemistry, Professor G. Dixon-Lewis, of the Department of Fuel and Energy, and Professor D. Bradley, of the Mechanical Engineering Department. At the present time it consists of 13 permanent staff members and 15 research students. My hosts during my visit were Professor D. Bradley and two members of his scientific staff, Dr. C. Sheppard and Dr. P. Gaskell. There is close coordination between the three departments forming this center. These ties are further strengthened by an interdisciplinary M.S. program in combustion and energy for which each of the three departments has well-defined teaching responsibilities.

Within the Mechanical Engineering Department there are four major research areas. These include: combustor testing and numerical models, turbulent explosions, dust explosions, and internal combustion engine studies. Approximately one-half of the research in the department is supported by the UK's Science and Engineering Research Council (SERC) and half through contracts with private industries such as British Leyland Technology Ltd., British Gas, and Rolls-Royce. Bradley told me that his research has been handicapped in recent years by the absence of any coherent anti-stokes Raman spectroscopy (CARS) or laser-induced fluorescence (LIF) equipment at the center. A CARS laboratory, costing upwards of \$750,000, has been requested from the SERC by a consortium of organizations including the University of Leeds, the Atomic Energy Research Establishment at Harwell, and Cambridge University. This lack of instrumentation is putting Bradley way behind laboratories in Germany and France which have long had such equipment.

Combustion Modeling

This work, directed by Gaskell, involves both tests and development of numerical models for three types of combustors: jet-stirred, tunnel (dump) burners, and gas turbine combustors. A recent activity involves a jet-stirred conical reactor where the results of a numerical calculation involving a higher order computational fluid dynamics (CFD) scheme in conjunction with a laminar flame model (provided by the Department of Fuel and Energy) were compared with the results of experiments. The geometry used in this work (shown in Figure 1) involves the flow of a low-speed (30 to 130 m/s) premixed jet of methane and air (0.6 equivalence ratio) into a domed 58° (included angle) expansion cone. The results of this work showed that the advantages of more refined turbulence modeling--Reynolds stress modeling (RSM) as compared with $k-\epsilon$ modeling--were only obtained when a higher order (QUICK instead of hybrid) CFD scheme was used. Although I did not see any experimental comparisons, it appeared that the predictions were reasonable. However, use of a laminar flame model limits their calculations to low to moderate strain-rate reactions, and, because of the lack of experimental data for more complex reactions, to rather simple fuels such as methane. To avoid numerical oscillations, sometimes encountered in higher-order methods in region of high velocity gradients, a monotonicity-preserving scheme was introduced similar to that employed in Boris' (NRL) flux-corrected transport

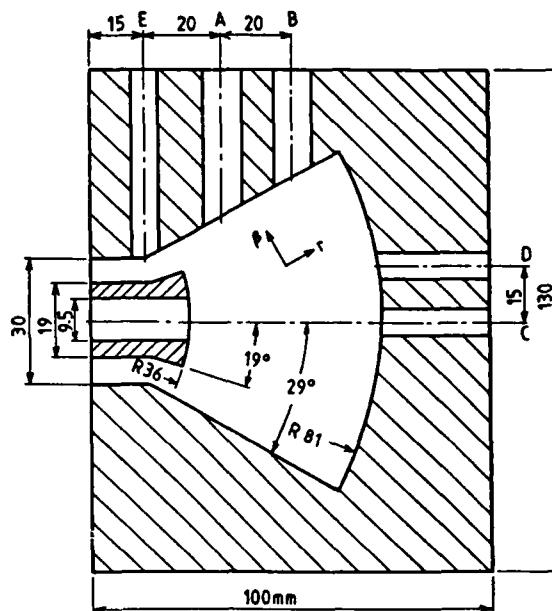


Figure 1. Leeds jet-stirred conical reactor.

(FCT) scheme. Although these calculations showed improvements when RSM was used in the cold-flow calculations, it was impossible to obtain a converged solution for the reacting flow case. Nevertheless, the study was successful, demonstrating that improvements in turbulence modeling can only be expected if they are used in conjunction with higher order CFD schemes. Experience with the QUICK scheme showed that a mesh-independent solution could be obtained with only 20 percent of the number of computational points required by the hybrid method. Finally, in conjunction with this work, Gaskell discovered a pentadiagonal-coupled solver for the momentum equation which yielded a 50-percent reduction in computational time.

Turbulent Explosions

Turbulent explosion experiments, directed by Mr. M. Lawes, were carried out in a glass-walled cylindrical reactor approximately 50 cm in diameter, stirred by four high-speed (10,000 rpm), 8-kw electric motors. The purpose of this work was to examine the effect of turbulence (root-mean-squared velocities up to 70 m/s can be obtained) on burning rate and burning velocity. In these tests, the region of isotropic turbulence was produced and then ignited by a single or dual spark arrangement, producing a spherical flame. Velocity measurements were made with a specially designed high-data-rate laser Doppler anemometry (LDA) system; heat release was measured by CH radical emission; and the flow was

visualized with a high-speed motion picture/schlieren apparatus. What was found was that just as in a laminar flame, stretching due to the presence of turbulence can cause flame extinction. The experimenters found that 60 percent of the reactants remained unburned behind the flame front. They are currently proposing research which will be directed toward obtaining knowledge and understanding of the mechanism by which this unburned fuel is eventually consumed. The principal accomplishment of this work appears to be the development of the turbulence level definition which allows the correlation of data obtained from both stirred reactor and burner tests.

Gas Turbine Combustors

This work, directed by Sheppard, involves the interaction of dilution jets with the core flow in an annular-type, gas turbine combustor. For this purpose a number of combustors have been built for hot- and cold-flow studies in which 5-hole probes and crossed hot-wire probes were used for the measurement of mean and fluctuated velocities. Methylene was used as a tracer in conjunction with a flame ionization detector for detecting the trajectory of the dilution jets. It was found that the velocity profile of the dilution jet at the wall of the combustor was extremely nonuniform and that the only way of including this effect was to modify the computational region to add the annular dilution-jet plenum. This modification is currently underway.

Internal Combustion Engines

This work, also directed by Sheppard, involves single cylinder, transparent head, internal combustion engines and is supported by British Leyland. Of particular interest is exploring the effect of torch ignition combustion enhancement in precombustor geometries of various designs. Similar to the turbulent explosion studies, it has been observed that sufficiently high flame stretching (in this case produced by the high turbulence levels of the torch ignition process rather than mechanical mixing) can produce a decrease rather than an increase in the burning rate. In these studies, ion probes are used in conjunction with conditional sampling in order to yield information on the nature of combustion (including knocking), to monitor the flame progress from the point of ignition, and to determine the amount of cyclic dispersion.

RESEARCH AND DEVELOPMENT ACTIVITIES IN FLUID MECHANICS AT ROLLS-ROYCE

The company now known as Rolls-Royce PLC, had its origins in the former Rolls-Royce Ltd., de Havilland, Bristol Siddeley, and Bristol Aeroengine companies. At Derby, UK, Rolls-Royce (RR) designs and produces gas turbine engines destined for the civilian and the commercial and private market. Approximately 2300 engineers are employed there. Military gas turbine engines are produced at the Bristol plant where 2000 engineers are employed. At present, RR has gas turbines in service with more than 1200 airline, military, and executive operators.

Our host on our recent visit to RR was Mr. P. Clark, assisted by Mr. A. Duncan at Bristol, and Mr. B. Lowrie at Derby, and approximately 15 others who joined us for various discussions. Clark is an important person in RR's research and development activities, since as Advanced Engineering Controller, he is responsible for more than \$150 million in company-funded research. Our main objective was to obtain a broad introduction to RR's research and development activities.

Research Organization and Funding

Research and development at RR is conducted in the so-called Theoretical Sciences Group (largely responsible for computational efforts), research groups dealing with individual technologies and the engineering sciences that enter into those technologies, and the Advanced Research Laboratory, which deals with the development and application of sophisticated measurement and diagnostic techniques and laser technology in addition to certain other specialized tasks.

A matter of great satisfaction and pride at RR is the close connection they maintain with the government laboratories and practically every university in the UK engaged in science and technology related to company interests. At this time, RR is funding through grants and contracts (including donation of facilities) nearly 15 universities in the UK and several in the US in addition to its funding of work at the Royal Aircraft Establishment at Farnborough, the National Gas Turbine Establishment (NGTE) at Pyestock, and the National Physical Laboratory at Teddington. In the UK, grants are made both for faculty and student research. In several cases RR employees, selected on merit by universities for graduate studies, are released for full-time study to work on a doctoral program that is considered, directly or indirectly, to be related to RR's interests.

Eugene F. Brown
12/9/86

Research Topics

The main research topics discussed were turbomachinery blading design, predictive schemes for combustors, unsteady processes in burners and after-burners, turbine blade cooling, and installation aerodynamics.

Combustors continue to present several interesting challenges. Both at Bristol and at Derby, discussions were held on various subjects:

- Phenomenology of mixing in primary zone and analogical experimental studies
- Fuel preparation through the use of atomizers and the so-called vaporizers
- Multimode behavior of swirl-stabilized flows
- Ignition at high flow speeds and the development of plasma ignitors for pulsed and continuous operation
- Combustor wall cooling taking into account wide- and narrow-band radiation
- Modeling of combustor flowfield
- Phenomenology and prediction of reheat buzz.

In several of these areas there is close collaboration between RR and various universities such as at Cambridge, Imperial College (London), and the University of Manchester Institute of Science and Technology.

In combustor modeling, although there seemed to be interest in advanced turbulence models, the code discussed was PACE, developed by Dr. W.P. Jones of Imperial College, with conventional turbulence modeling. It is a matter of some interest, if not of concern, that there is practically no research group receiving funding in the US for development of conventional turbulence models. PACE, a TEACH-like code that employs hybrid differencing, is capable of modeling two- and three-dimensional steady, recirculating, turbulent reacting flows. It is a TEACH-like code and employs hybrid differencing.

An area of considerable importance, but with little guidance through direct measurements, is the nature of development of structural length scales in the combustor flowfield. This has an obvious impact on turbine nozzle flowfield and the wakes interacting with the rotor blades. People in both the combustion and turbine groups at RR discussed the subject with us.

The phenomenology associated with the development of recirculation zones in swirl-stabilized primary zone flows in combustors is largely unexplained. Multimode behavior has been observed at RR. Influence of radial momentum is suspected to be responsible for modal changes.

The manner in which swirl is produced by "S-shaped" ducts was discussed. Swirl imparts flow uniformities at the engine inlet which reduce the stall margin. Efforts are underway to determine the mechanism by which this swirl is produced. Some measure of control is provided in the Tornado fighter by the use of so-called fences on both the bottom and side walls. They are in the nature of flow blockers and not vortex generators and have the effect of altering the circumferential distortion to a radial one which the engine can tolerate much better. Sir John Seddon, former Director-General of Research (Air) at the Ministry of Defence, currently associated with the University of Bristol, has consulted with RR on this problem. Research at Cambridge University on distortion is also supported by RR.

Computational Fluid Dynamics (CFD)

RR's CFD activities are directed by Dr. Peter Stow, head of the theoretical sciences group at Derby. Currently 11 people work with Stow at Derby and another four in Bristol. RR has their own IBM 3081/3090 system and it links with the Cray X-MP at Cray's Bracknell (UK) facility and with Boeing's Cray X-MP in Seattle. Among the topics being investigated in Stow's group are a blade aerodynamics/turbine heat transfer, installation aerodynamics, boundary layer coupling, base-flow modeling, transition modeling, flutter, Navier-Stokes solvers, and blade/wake interactions. For this purpose they have used the time-marching codes of Ni and Jameson, the Moore elliptic flow program (Moore and Moore, 1984) the linearized ANSI code developed by Top Express, the nonlinear unsteady code of Denton (1982), and the FANCI code developed by MIT.

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S.N.B. Murthy
 School of Mechanical Engineering
 Purdue University, and
 Eugene F. Brown
 2/09/87

CONTROL THEORY AT THE UNIVERSITY OF STUTTGART

The University of Stuttgart, West Germany, has 13 fakultäts (schools or faculties) and a student body of about 17,500 with a total of 520 professors. A new campus outside of town has recently been constructed so there are quite adequate and modern facilities.

Basic controls is taught to students in mechanical engineering (about 2000 students), chemical engineering (about 1000) and technical cybernetics (about 200). In West Germany, this latter discipline is only taught at Stuttgart. Each of the faculties of the university has numerous institutes, each led by a principal professor. I visited two institutes, the first one in the Process Engineering Faculty (Verfahrenstechnik), the second one in the Electronics Faculty.

The Process Engineering Faculty

The Process Engineering Faculty's Institute for System Dynamics and Control Theory is led by Professor Ernst-Dieter Gilles. My host for the visit was Dr. J. Raisch, and I also talked to Professor M. Zeitz of the institute. The instructional program is typical of that at a good American school. There are two control theory courses, the first treating classical SISO systems and the second the state/space approach. Other courses consist of distributed parameter systems, control of distributed parameter systems, signal processing, dynamics of chemical systems, simulation, and laboratory exercises. About the only surprise here is the emphasis on distributed parameter systems and the chemical systems course. This emphasis is connected to chemical processes--one of the basic research thrusts of the institute. About 20 assistants work on the various research projects, five of them supported by the state (Baden-Wurtemberg) and the remaining 15 principally by Deutsche Forschungsgemeinschaft (DFG).

There are three main research activities of the institute. The first one concerns modeling and control of chemical processes, particularly process control of catalytic fixed-bed reactors. The catalytic reactor is a distributed parameter system and is also highly nonlinear; therefore the control procedure is not trivial. The laboratory has a 10-meter-high distillation column which is used for the investigations. In the polymerization of complex molecules they are using Kalman filter techniques to reconstruct from measured temperatures and refraction the chain-length distribution. Since one of the main concerns in chemical processing is the early detection of

hazardous states in chemical plants, the investigators are working toward early detection of such states by the use of parallel filtering networks. There is also an effort in dynamic simulation of chemical plants using the DIVA computer program among others. This work is largely experimental and there are a number of excellent experimental arrangements and supporting data.

Automation of inland waterway shipping is the second area of their research (it is funded by DFG). The project team's first idea for automatic steering involved an inductance cable which was to be laid on the river bottom. However, interference effects and the economics of laying the cable led the team to consider radar, which is used to extract information about the river bank and objects on the waterway. From the measured information a reference course is generated and from this, automatic course-keeping can be developed. Semiautomatic operation is possible by the use of a multiple-target traveling algorithm. From the return radar signals the pilot would need to interpret the object as a ship, island, clutter, buoy, or other, and he could take appropriate rudder action. I saw a video tape of runs of their experimental ship, which is now functioning on the Neckar river. One could see the difficulties in interpreting the radar signal. The current focus of the research is on the development of a safe, automatic navigation system in the presence of a large number of ships.

The institute has also been involved in the control of the aiming of radio telescopes. This has consisted of work for control of a telescope in Spain and for the telescopes of two industrial concerns.

The theoretical work of the institute is directed at control theory of distributed systems. Professor Zeitz, in particular, is interested in canonical forms for nonlinear systems (Zeitz, 1984). Other researchers are investigating parallel filter algorithms.

I was impressed by the experimental activity of the institute and believe they have a nicely integrated teaching and research program. There also seemed to be a close connection to industry, and therefore some proprietary information in their research.

The Electronics Faculty

In the Electronics Faculty I visited the Institute for Control Theory and Process Automation, which is headed by Professor R. Lauber. My host for the visit was Dr. E. Kurz. The principal effort of the institute appears to be in the area of the application of software to the

characterization of the development and project management specifications in large-scale projects. The software package used in this process is EPOS, which is a German acronym based on the objective of the work. Since 1980 EPOS has been used on a variety of development projects. There are over 80 installations using the package. Two applications of the system are:

- Control and navigation system for an aircraft (Drtil, 1984)
- Motor vehicle systems (Dais et al., 1984)

There is a publication *EPOS Kurzbeschreibung* (1985) (in German) which is available from the institute. This publication outlines in some detail the structure of the software package. A given project is conceived of as consisting of three parts--project management, product management, and development. Very specific interactions of different subsystems can be included in the model. The software creates more than project flow charts. System control laws can be automatically generated in higher programming languages such as C/ATLAS. A source file in PASCAL or ADA can also be partly automatically generated. A demonstration of EPOS which was concerned with the description of a heat transfer system and its proper design showed some of the graphical aspects of the program. The software organization is open-ended and I believe that more graphical capability is presently being included in the package.

EPOS is available as a commercial package from the institute. All the references that I have describing EPOS are in German. Some of the key words in the EPOS sublanguages are also given in English. The automatic code generation in PASCAL or ADA would be in those languages and should not present any difficulty. I have several references (in English) on the applications of the system which I would be happy to pass on to anyone. I also believe that one or more packages are presently being used in America.

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Daniel J. Collins
2/12/87

FLUID MEASUREMENT CAPABILITY AT THE INSTITUTE FOR HYDRAULIC ENGINEERING AND WATER RESOURCES DEVELOPMENT, AACHEN, WEST GERMANY

My visit to the Institut für Wasserbau und Wasserwirtschaft (IWW), directed by Professor G. Rouvé, was motivated by an article on turbulent structures in separated flows (Schulte and Rouvé, 1986). The institute was founded in 1926 and presently occupies buildings in the center of Aachen, West Germany, somewhat separate from the RWTH University of Technology. There are five professional people with 13 support people and about 30 students in the institute.

My host for the meeting was Diplome-Engineer H. Schulte; I also talked to Diplome-Engineer U. Arnold. I was impressed with the complete computerization of the laboratory. All data-taking is tied in with a central computer (Prime 250 II). At present six Apple II and IIe PC's are used for data-processing and experimental control. The IIe units are shortly to be replaced by IBM PC AT's or equivalent. Seven terminals and a graphic terminal are connected to the Prime computer. For extensive calculations there are lines to the university central computer (CDC Cyber 175, Vax 11/780, FPS 164) and there is also a line to a Cray 2 at the Nuclear Research Center at Jülich.

The institute's experimental equipment consists of four tilting flumes, a cavitation channel, pipe flow model, low-speed wind tunnel, and several meander models. In addition to the standard flow measurement equipment there are two laser Doppler velocimeter (LDV) systems, one of them consisting of two channels and a digital image processing system which is being used in a very innovative manner.

Some of the experimental measurements on the turbulent structure reported by Schulte and Rowe (1986) are shown in Figure 1. Comprehensive measurements on 1180 points were made in the separated flow at high Reynolds numbers. With respect to the mean velocities, Reynolds stresses, and large-scale motion the whole flow field shows a regular structure. Correlation measurements indicate spatial distribution of the large-scale structure. It would be productive if further measurements were made using

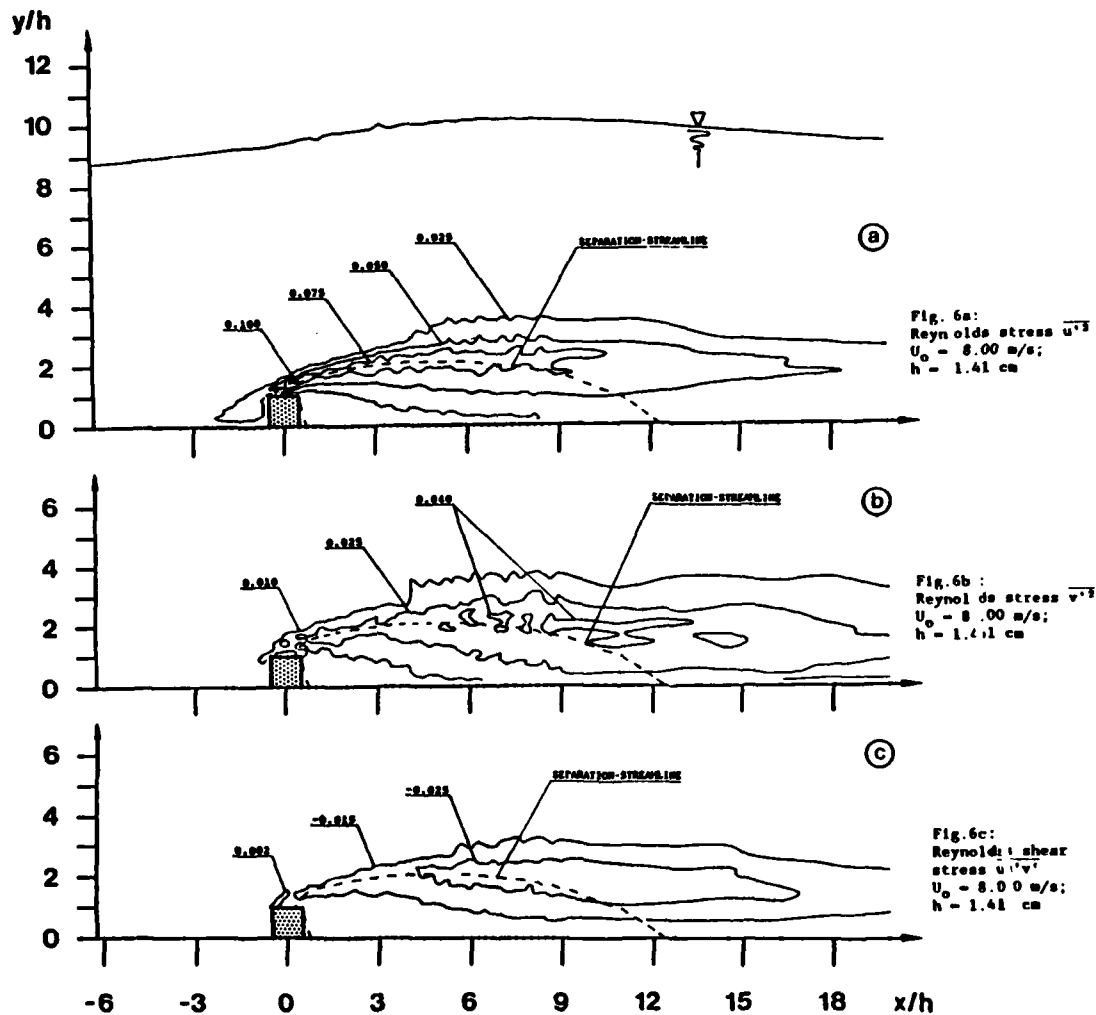


Figure 1. Some experimental measurements on IWW's turbulent structure.

particle image velocimetry (PIV) on the same experiment and then make comparisons of the instantaneous values with the mean values, but instantaneous measurements are apparently not contemplated at the present time. Somewhat the same physical setup is now being used in extensive cavitation measurements using LDV, and the Institute will report soon on this work. The efficiency and speed of the computer-controlled setup on a current experiment was impressive.

The institute's image processing technique is used to obtain a complete flow field characterization or visualization rather than a single-point measurement as in the case of LDV (Haenscheid et al., 1985; and Arnold et al., 1985). Thus, the purpose is in a sense the same as that of PIV's but the approach is very different and the data reduction is digital and fully automatic.

Image processing is approached in two ways (Haenscheid et al.). The first way involves the use of small light-reflecting particles on the surface of the water. This approach, except for the modern digitization equipment is similar to that done by Prandtl years ago. Figure 2, taken from the reference, shows the experimental setup and the associated equipment. More interesting is the second technique in which fluorescent dye solution is injected into the fluid and then activated by UV-A-light (black light--blue tubes). Measurements are performed simultaneously at multiple points in real time without the disadvantage of influencing the flow field by probes. Thus, image processing, applicable for investigations where conventional flow measurement methods fail, can add significant new capability to existing measurement instrumentation in a hydraulic laboratory.

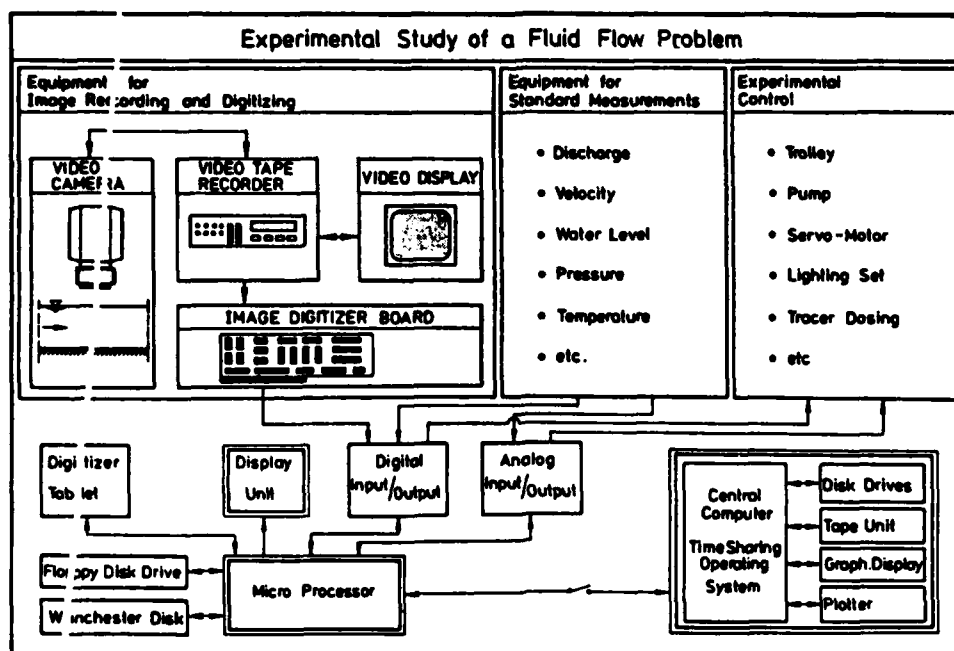


Figure 2. Experimental environment for hydraulic research studies at IWW using image processing technique.

An application of this technique is given in the study on mixing flows in rivers (Arnold et al., 1985). The video concentration measurement system combined with the digital imaging processing is a powerful technique (the obtained visualization of the flow on the video screen is impressive). The transverse mixing coefficient, transverse dispersion coefficient, and the turbulent intensity for the two-dimensional flow can be obtained. This latter work was funded by the German Research Foundation which is equivalent to the NSF.

In addition to the large experimental effort at the institute there is also a corresponding theoretical investigation of the flow. Pasche et al. (1985) have given an overview of overbank flow models with some comparison to experiments for different eddy viscosity models. During the next year Pasche (visiting from the University of California at Davis) will investigate numerical models in comparison with the data being generated at the laboratory.

IWW is a small but dynamic unit using very modern experimental methods to investigate fluid flows. I think that the digital imaging process has great merit and this technique should generate some interesting results in the coming years.

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- Arnold, U., E. Pasche, and G. Rouvé, "Mixing in Rivers With Compound Cross-Section," *Proceedings from the International Association for Hydraulic Research 21st Congress* (Melbourne, Australia, 1985).
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- Pasche, E., U. Arnold, G. Rouvé, and M. Asce, "A Review of Overbank Flow Models," (internal publication, 1986).
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Daniel J. Collins
2/13/87

INTERNATIONAL CONFERENCE ON ANOMALOUS RARE EARTHS AND ACTINIDES

This conference, held from 7 through 11 July 1986 in Grenoble, France, had 350 participants from 22 countries. There

were no parallel sessions and the time was divided between oral, invited presentations of 15 to 40 minutes, and contributed poster presentations. Selected papers from the posters sessions were discussed as part of the oral sessions.

There is considerable continuity in this field. J. Friedel (Université de Paris-Sud, Orsay, France) opened the conference by giving a historic overview on topics which included whether the magnetic moments were primarily localized or itinerant and the origin of the high effective mass, m^* . Some of the subjects covered in the conference were a continuation of work that has been going on for many years. For example there were papers on the Kondo effect and on the interplay of superconductivity and magnetism, a subject that includes the important prediction of gapless superconductivity by Abrikosov and Gorkov in 1961. Other subjects, such as heavy-fermions and heavy-fermion superconductors, are much newer. However, most of these newer subjects also evolved from the earlier ones. For example, nearly 20 years ago it was suggested that the effective magnetic moment of concentrated systems--e.g., the element Ce--might be reduced in much the same way as in dilute alloy Kondo systems. This suggestion has turned out to be correct. One can understand some of the properties of heavy-fermion systems by thinking of them as Kondo systems. For example, one of the characteristics of dilute Kondo alloys is that the impurity contribution to the specific heat is linear in temperature at low temperatures. It was pointed out at the conference that if one can scale up the coefficient of this linear term to high concentrations, then the coefficient will be large enough that the system can be classified as a heavy-fermion system.

The unusual properties of heavy-fermion superconductors have stimulated increased interest in this general area. In heavy-fermion superconductors, CeCu_2Si_2 , UPt_3 , and UBe_{13} , specific heat measurements show that the electrons involved in the transition are from a part of the Fermi surface with a very high density of states. Because the electrons involved have a very high effective mass, it is believed that only the f electrons can give rise to such a high density of states. The unusual properties of the heavy-fermion superconductors were reviewed at the conference by A.J. Leggett (University of Illinois at Urbana-Champaign) and B. Batlogg (AT&T Laboratory). Leggett compared the heavy-fermion superconductors to superfluid ^3He . Both have large-effect masses and strong short-range repulsive forces. They differ in that one is charged and the other un-

charged. ^3He has both Galilean invariance and rotational symmetry while the heavy-fermion superconductors have neither. Spin-orbit coupling is negligible in ^3He and large in heavy-fermion superconductors. Batlogg reviewed the considerable evidence provided by specific heat, ultrasound, and nuclear magnetic resonance (NMR) relaxation for an anisotropic energy gap. He also presented evidence which suggests that there are spin density waves in $\text{U}_{0.95}\text{Th}_{0.05}\text{Pt}_3$.

Before this conference the existence of heavy electrons in heavy-fermion systems had only been inferred from measuring such quantities as $C/T=\gamma$, where C is the specific heat, in the limit $T \rightarrow 0$. Standard theory predicts that γ is proportional to m^* . The highlight of the conference was the first reports of the direct measurement of heavy electrons in CeCu_6 and UPt_3 . L. Taillefer et al., from the Cavendish Laboratory, UK, discussed their observation of de Haas-van Alphen oscillations in UPt_3 . The measurements required low temperatures, 0.02 K, and high magnetic fields, 115 kOe. The frequency of these oscillations determines the cross-sectional area of the extremal orbits of the Fermi surface. The amplitude of these oscillations contains a factor of the form $\exp(-Am^*T/H)$ where A is a known constant. This allows one to determine m^* by measuring the temperature dependence of the amplitude. The electrons in the six orbits they observed all had heavy masses--i.e., for all orbits, $m^* \geq 25m_e$. The observed orbits agree with the two density functional calculations by T. Oguchi et al. (Northwestern University, Evanston, Illinois) and by C.S. Wang et al. from the Naval Research Laboratory. These theories correctly predict the orbits but not the large values of m^* . M. Springford et al. (University of Sussex, UK) presented their de Haas-van Alphen results on CeCu_6 . They reported observing heavy masses (approximately 80 m_e), very low velocities, and long mean free paths (approximately 10^3 lattice spacings). Neither group reported seeing any light masses.

In a Kondo lattice there is a competition between having a magnetically ordered ground state and having a nonmagnetic ground state. The nonmagnetic state can arise if the conduction electrons and the local magnetic moments form singlet ground states. It is said that the conduction electrons compensate the local magnetic moments. If the negative exchange coupling between the local magnetic moments and the conduction electrons is larger than a critical value, then the ground state will be nonmagnetic. C. Lacroix (Centre National de la Recherche Scientifique [CNRS], Grenoble, France)

pointed out that the current theoretical critical value for the exchange coupling is almost an order of magnitude larger than experiment. She discussed possible deficiencies in the theory. For example, in the current theory this coupling is isotropic. If one includes anisotropy then the theoretical prediction might be lower. More fundamentally, charge fluctuations might invalidate the Kondo lattice model. Another question she raised was the possibility that there might not be enough conduction electrons to compensate all the local moments.

O. Vogt (ETH, Zürich, Switzerland) pointed out that, because the magnetic properties of rare-earth and actinide compounds are usually anisotropic, it is very desirable to use pure, well characterized, high-quality, single crystals. He then discussed methods of ultrapurification (sublimation, vacuum melting, zone refining, and electrotransport) and crystal growth (solution growth, mineralization, Czochralski, and Bridgeman). Rare-earth oxides, produced by ion-exchange columns, can be obtained having 5N purity. In general, to convert the oxides into metals one uses hydrogen fluoride to convert the oxides into fluorides, and then the fluorides are reduced to the pure metallic state with calcium. Research on the actinides has been hampered by the toxicity, reactivity, scarcity, and radioactivity of these elements. These undesirable properties make it necessary to work in glove boxes.

Point contact tunneling spectroscopy has been used for several years to study these systems because it has good energy resolution. This spectroscopy has the disadvantage that the spectra is difficult to interpret. P. Wyder (Max-Planck-Institut für Festkörperforschung, Grenoble, France) reviewed both the experimental and theoretical progress that has been made in understanding point contact spectroscopy.

In his epilogue on the theory T.M. Rice (ETH, Zürich) discussed the $1/N$ expansions (N is the multiplicity) and the effect of hybridization. He pointed out that workers are beginning to be able to do realistic bandstructure calculations. For example, as mentioned above, Oguchi et al. and Wang et al. have performed such calculations on UPt_3 . There is still a need to be able to calculate the parameters in the Anderson Hamiltonian and then to use these parameters to self-consistently calculate the quasi-particle bands. One hopes that this will lead to a large renormalization of m^*/m but will not change the shape of the Fermi surface, since, as discussed above, the predicted Fermi surface agrees with experiment. The superconductivity is probably

due to an electron-electron interaction and not an electron-phonon interaction as it is in more conventional superconductors.

In summarizing the experimental papers F. Steglich (Institut Festkörperfysik, Darmstadt, West Germany) pointed out that new techniques such as de Haas-van Alphen, Hall Effect, ultrasound, neutron scattering, NMR, Mossbauer, far infrared spectroscopy, and improved photoemission spectroscopy have clarified our understanding of anomalous rare earths and actinides. At the same time, our ability to fabricate them has improved. For example, people reported fabricating single crystals of UPt_3 and $CeCu_6$ with resistance ratios of 800 and 150 respectively. Other workers have produced films of $CeCu_2Si_2$ with superconducting transition temperatures equal to those obtained in bulk samples.

Alan S. Edelstein
Metal Physics Branch
Naval Research Laboratory
3/4/87

A NEW RAPID-PUBLICATION, SHORT-PAPER JOURNAL ON LOW-DIMENSIONAL SYSTEMS

Gordon and Breach announced that in early 1987 it will begin publication of a journal, entitled *Low Dimensional Systems*. This publication, carrying 5-6 page long articles (submitted in a camera-ready form) will aim at a turn-around of 8 weeks from acceptance. It will provide a very rapid means to communicate new results in the area of semiconductor-based structures (such as heterojunctions, superlattices, and lithographically defined layers). Occasionally papers on other types of systems and relevant basic surface- and interface-physics will also be accepted. It must be emphasized that the journal will consider only topics in general areas of fundamental physics and of truly new engineering concepts, rather than detailed device work of a more applied nature.

The editors are Dr. R. Nichols (Oxford), Professor T. Ando (Tokyo), Professor E. Gornick (Innsbruck), and Professor B.D. McCombe (Buffalo), and prospective authors are asked to submit manuscripts to the appropriate regional editor. For US scientists, the address of Professor McCombe is: Department of Physics and Astronomy, SUNY, Fronczak Hall, Buffalo, New York 14260.

Prospective American subscribers should ask for information from Gordon

and Breach Science Publishers, Marketing Department, P.O. Box 786 Cooper Station, New York, New York 10276.

Paul Roman
2/25/87

X-RAY SENSOR LIFTED INTO ORBIT IN FIRST ANGLO-JAPANESE SPACE VENTURE

The British National Space Center announced the successful launch on 5 February of a satellite carrying the largest-ever x-ray sensor. This marks the first Anglo-Japanese collaboration in space and enables the study of some of the most exotic and powerful objects in the universe.

The sensor, known as a large area counter (LAC), weighs over 100 kg and has a sensitive area of 0.5 m². It was launched on a Japanese ASTRO-C satellite from the Kagoshima Space Center, Japan. As of this date, the detectors are switched on and all systems are functioning normally.

The project is the result of collaboration between research groups at the British National Space Centre's (BNSC) Rutherford Appleton Laboratory (Space Department), the University of Leicester, the Tokyo Institute of Space and Astronautical Science, and the University of Nagoya.

Hundreds of bright cosmic x-ray sources, discovered with earlier satellites such as Ariel 5 and EXOSAT, have been identified with binary star systems and quasar-like galaxies. A common feature of many, if not all, of these most powerful x-ray sources is that they contain a region of extreme gravity. Almost certainly this strong gravitational field is due to a neutron star or (in the case of the quasars) a massive black hole. Dust, gas, or even whole stars pulled into these "gravity wells" causes the release of the observed x-radiation.

By its sensitivity, the LAC ASTRO-C will allow these x-ray signals to be monitored with greater precision than ever before, thus revealing important new information on the nature of the emitting objects.

ASTRO-C is the only active in-orbit observatory for x-ray astronomy available to astronomers worldwide.

C.J. Fox
2/23/87

ONRL COSPONSORED CONFERENCES

ONR, London, can nominate two registration-free participants in the conferences it supports. Readers who are interested in attending a conference should write to the Scientific Director, ONRL, Box 39, FPO New York 09510.

Natural Mechanisms of Surface Generated Noise in the Ocean, La Spezia, Italy, 15-19 June 1987.

International Symposium on Polymer Electrolytes, Fife, Scotland, 17-19 June 1987.

First International Conference on Industrial and Applied Mathematics, Paris, France, 29 June-3 July 1987.

The Physics and Technology of Amorphous SiO₂, Les Arcs, France, 29 June-3 July 1987.

Science and Technology of Fast Ion Conduction, Les Arc, France, 1-15 July 1987.

Phase Transformation, Cambridge, UK, 6-10 July 1987.

6th International Conference on Composite Materials (ICCM-ECCM), Imperial College, London, UK, 20-25 July 1987.

5th International Conference on Phase Partitioning, Oxford University, UK, 23-28 August 1987.

7th International Conference on Erosion by Liquid and Solid Impact, Cambridge, UK, 6-10 September 1987.

International Symposium on Turbulent Shear Flow, Toulouse, France, 7-9 September 1987.

7th GAMM Conference on Numerical Modeling in Fluid Mechanics, Louvain-la-Neuve, France, 9-11 September 1987.

ONRL COSPONSORED WORKSHOPS

ONR, London, can nominate registration-free participants in the workshops it supports. Readers who are interested in attending a workshop should write to the Scientific Director, ONRL, Box 39, FPO New York 09510.

Transverse Effects in Optical Bistability and Instabilities, Lucca, Italy, 7 August 1987. (Roman)

US-France Workshop on Turbulent Reactive Flows, Rouen, France, 11 August 1987. (Brown)

ONRL REPORTS

To request reports, indicate the report number (in parentheses after the title and author's name) on the self-addressed mailer and return it to ONR, London.

Biological Sciences

Molecular Biology: Conference on Genetic Engineering Techniques, by Claire E. Zomzely-Neurath. (7-009-C) The topics covered at this conference included the synthesis of foreign products in *E. coli*, expression of cloned genes in yeast and cultured mammalian cells, the introduction of cloned genes into whole animals and plants, and studies on a number of specific genes which have a significant clinical potential. Presentations on these topics are summarized.

REPORTS ON EUROPEAN SCIENCE AND TECHNOLOGY FROM OTHER COMMANDS

Information on each of the reports listed below was furnished by the activity whose name and address is provided in brackets. For further information on any report, contact the originating activity.

Aeronautics

Flight-Test Results from the EAP, a report by LTC Robert C. Winn, European Office of Aerospace Research and Development. (3 pp) [Report No. EOARD LR-87-02. European Office of Aerospace Research and Development, Box 14, FPO, New York 09510.]

The Royal Aeronautical Society hosted a lecture titled "EAP--Initial Flight Test Results" on 22 January 1987. The lecture covered the history of the EAP (Experimental Aircraft Program), the new technologies demonstrated in the aircraft, some results of the flight test program, and an indication of how the EAP will lead to the European Fighter Aircraft. It was presented by the Chief Test Pilot for British Aerospace. This report is a summary of that lecture.

HOTOL Meeting Held, a report by LTC Robert C. Winn, European Office of Aerospace Research and Development. (3 pp plus 7-page enclosure) [Report No. EOARD LR-86-134/LDV. European Office of Aerospace Research and Development, Box 14, FPO, New York 09510.]

The Royal Interplanetary Society recently hosted a meeting on HOTOL (horizontal takeoff and landing), British Aerospace's entry into the reusable spacecraft world. The meeting brought together all of the principal players in the HOTOL effort. The report includes a summary of the meeting, a list of speakers, and an article on HOTOL which appeared in British Aerospace's company magazine.

Biological Sciences

A Tomography-Like Real-Time Imaging of Neuronal Activity in the Intact Brain, a progress report by Amiram Grinvald, Weizmann Institute of Science, Israel, under grant no AFOSR-85-0301. (9 pp) [Report No. EOARD TR-86-09. European Office of Aerospace Research and Development, Box 14, FPO, New York 09510.]

The use of voltage-sensitive dyes and of optical recording of neuronal activity is a potentially powerful technique for investigating the development, organization, function, and recovery from malfunction of the mammalian cortex *in vivo*. The major advantage of optical recording is the feasibility to record single cells or population activity, from thousands of loci, simultaneously.

During the first year of this study, the necessary technological developments were emphasized. In addition to the optical imaging with voltage-sensitive dyes, having a millisecond time resolution, it was found that slow intrinsic signals facilitate optical imaging of the functional architecture of cortex, without the use of any dyes. These two techniques have major advantages over current anatomical and physiological techniques. As a result, the techniques are now mature for the investigations we proposed on the visual cortices of cat and monkey.

In addition, the optical methodology was also used to address biological questions related to the normal and pathological function of CNS myelinated axons.

New voltage-sensitive dyes were designed and synthesized for iontophoretic injection into single cells. With this approach for the first time, the feasibility and recording of postsynaptic potential from dendritic processes *in situ* was demonstrated. The same probes were also used for a second application; extracellular injection of these dyes in conjunction with retrograde and/or anterograde labeling of specific pathways in the brain have been demonstrated.

Chemistry

Life Sciences Liaison Visit, Prins Maurits Laboratory (TNO), Rijswijk, Netherlands, a report by MAJ Jim McDougal, European Office of Aerospace Research and Development. (2 pp plus 9-page list of the Chemical Laboratory's reports.) [Report No. EOARD LR-87-10. European Office of Aerospace Research and Development, Box 14, FPO, New York 09510.]

Scientists at Prins Maurits Laboratory of the Netherlands Organization for Applied Scientific Research (TNO), are working on protection of humans against toxic substances, especially chemical warfare agents. They have developed nerve agent alarms, detection devices, and a mobile unit which can purify 3500 liters of water an hour from chemical agent and radioactivity-contaminated water. They are leaders in the development and testing of individual and collective protection equipment. Risk assessment is accomplished by computer simulation of chemical attack and the effect of protective clothing.

Liaison Visit to Bern, Switzerland: University of Bern, a report by MAJ Scott A Shackelford, European Office of Aerospace Research and Development. (3 pp) [Report No. EOARD LR-87-03. European Office of Aerospace Research and Development, Box 14, FPO, New York 09510.]

Solid polymerization of a special "push-pull" diacetylene monomer class is proposed by Professor Markus Neuenschwander, Head, Institute for Organic Chemistry, University of Bern, Switzerland. Neuenschwander and his group have extensive experience in the study of highly conjugated aliphatic compounds, especially with the cyclic fulvene and fulvalene compounds. He and his group were also the first to synthesize a special class of electronic "push-pull" enamine-type diacetylene monomers several years ago. He plans to use past experience with these conjugated systems to synthesize properly oriented stacked "push-pull" diacetylene crystals for subsequent solid-state polymerization. This could produce a highly oriented conjugated solid polymeric network which may possess a low activation energy in optical absorption and electron transport processes. The fundamental molecular parameters necessary to produce the appropriately oriented diacetylene stacked crystal orientation as a function of optical absorption and electron transport properties will be characterized.

Environmental Sciences

Improvements in Empirical Modelling of the World-Wide Ionosphere, a final report by Professors Kurt Suchy and Karl Rower, Universität Düsseldorf, West Germany, under grant no AFOSR-83-0369. (15 pp) [Report No. (none assigned). European Office of Aerospace Research and Development, Box 14, FPO, New York 09510.]

After a method proposed by BOOKER one might describe the ionospheric electron density profile in a fully analytical way by using Epstein-functions. Since the practical application of this idea runs into serious difficulties a way out from these is indicated. A combined function, LAY, is introduced which allows the particular peak condition to be automatically respected. A larger set of empirical profiles measured in West Germany were analyzed and conclusions drawn how the function parameters could be determined for profile modeling. Numerical proposals are made with this in view. While these profiles are for the middle ionosphere, similar analysis is also executed for typical lower ionosphere profiles, and representative parameters are given.

Material Sciences

Material Research at the Fraunhofer Institute, a report by LTC Jim Hansen, European Office of Aerospace Research and Development. (1 p) [Report No. EOARD LR-86-125/LDS. European Office of Aerospace Research and Development, Box 14, FPO, New York 09510.]

West Germany's Fraunhofer Mechanics of Materials Institute has been very active in several areas of materials research. They are currently conducting high-temperature fracture and fatigue tests on ceramics. This work is being conducted in a new division devoted entirely to ceramics. They have also been able to produce some interesting materials using explosive compaction.

Ceramics and Composites in Turbine Engines, a report by LTC Jim Hansen, European Office of Aerospace Research and Development. (1 p) [Report No. EOARD LR-86-126/LDS. European Office of Aerospace Research and Development, Box 14, FPO, New York 09510.]

The DFVLR Institute for Structural Research and Design Development in Stuttgart, West Germany, has developed an impressive ceramics and composites design and testing facility. They have been applying their expertise to the design and testing of turbine engine components made of exotic materials.

Physics

MHD Energy Conversion, a report by MAJ Mel Townsend, European Office of Aerospace Research and Development. (2 pp) [Report No. EOARD LR-86-130/LDE. European Office of Aerospace Research and Development, Box 14, FPO, New York 09510.]

The Electrical Engineering Department of Eindhoven Technical University, the Netherlands, has a novel research center in magnetohydrodynamics (MHD). This multi-million-dollar laboratory has sustained an electrical power output of 735 kW for 10 seconds. The researchers at Eindhoven claim that this is the highest continuous power output ever achieved outside the Soviet Union. The report consists of a description of their MHD project and a discussion of the limited funding of this program.

SCIENCE NEWSBRIEF FOR MARCH

The following issue of *Science Newsbrief* was published by the ONR, London, Scientific Liaison Division during March. *Science Newsbrief* provides concise accounts of scientific research developments, meeting announcements, and science policy in Europe and the Middle East. Please request copies, by number, from ONR, London.

Number

Title

5-4 EUROSensors: Third Conference on Sensors and Their Applications, by Louis Cartz

FEBRUARY AND MARCH MAS BULLETINS

The following *Military Applications Summary (MAS) Bulletins* were published by the ONR, London, Military Applications Division during February and March. The *MAS Bulletin* is an account of accomplishments in European naval research, development, test, and evaluation. Request copies of the *Bulletins*, by number, from ONR, London.

Number

Title

7-87 Franco-German Supersonic Anti-Ship Weapon System--A.N.S.
 8-87 Foreign Weapons Evaluation (FWE) and NATO Comparative Test Programs (NATO CTP)
 9-87 Vosper Thronycroft Controls
 10-87 Conference Alert

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