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SYMPOSIUM REPORT

Symposium to honour Lennart Rodén

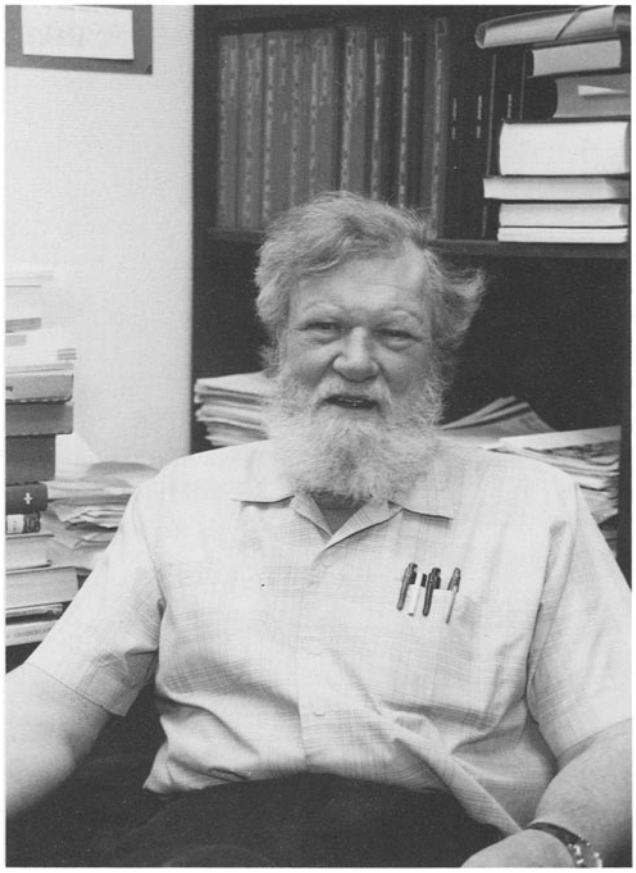
Glycosaminoglycans and connective tissue during the Rodénian era

An international symposium entitled *Glycosaminoglycans and Connective Tissue during the Rodénian Era* was held in Birmingham, Alabama, on November 13–14, 1994. It was organized to honour Lennart Rodén, one of the most respected scientists of his generation in the field of connective tissue polysaccharides. It is significant that about 100 scientists from eight countries assembled with only 3 months notice to pay tribute to Lennart. Many more would have liked to be there.

Lennart Rodén was born on 16 November 1929, and the symposium was thus held on the occasion of his 65th birthday. He grew up in Sweden and studied Chemistry at the University of Uppsala before entering medical school at the Karolinska Institute in Stockholm in 1949. During his medical training he enrolled as a junior instructor at the Chemistry Department in the laboratory of Professor Erik Jorpes. It was not uncommon at that time that the students, in parallel with their studies in medicine, also spent their spare time in a research department and this often became the beginning of a research career. In Lennart Rodén's case Biochemistry became his prime interest and he received his PhD in Medical Sciences in 1956 long before he finished his MD in 1962.

Lennart's doctoral work, under the guidance of Harry Boström and Sven Gardell, concerned the activation of the biosynthesis of chondroitin sulfate and keratan sulfate by glutamine and provided evidence, albeit indirect, that glutamine is the source of the hexosamine amino groups in vertebrate tissues. This was the start of a lifelong devotion to the structure and biosynthesis of connective tissue polysaccharides. Both Boström and Gardell, now retired professors in Internal Medicine and Medical and Physiological Chemistry, respectively, came to the symposium in Birmingham.

After his thesis work Lennart Rodén spent a postdoctoral year with Albert Dorfman at La Rabida-University of Chicago Institute as a Fellow of the Variety Club of Illinois and then served for 3 years as assistant professor (docent) in Medical Chemistry at the Karolinska Institute and the University of Uppsala. In 1961, he emigrated to the USA and worked for 11 years at the University of Chicago where he became Professor in the Departments of Pediatrics and Biochemistry. Since 1972 he has been Professor of Medicine, Dentistry and Biochemistry at the University of Alabama at Birmingham.



Lennart Rodén received an honorary degree in Medicine from the University of Uppsala in 1983.

At the end of the 1950s it was known from the work of Helen Muir that chondroitin sulfate, freed from proteins by proteolytic digestion, still contained traces of the amino acid serine. Lennart Rodén discovered in the beginning of the 60s that serine was likewise present in heparin, provided that the polysaccharide had not been subjected to bleaching in the course of the manufacturing process. This finding indicated that heparin was synthesized in protein-bound form and led to a search for the native heparin and heparan sulfate proteoglycans. He also discovered that heparin and the galactosaminoglycans (chondroitin 4- and 6-sulfate, dermatan sulfate) were

bound to serine via a trisaccharide containing two galactose residues and the unusual sugar xylose. This was one of the great breakthroughs in connective tissue research and it opened up the whole field of proteoglycan chemistry.

Another very important observation was the discovery that many connective tissue polysaccharides are not homogeneous polymers as previously believed. Lennart Rodén and collaborators showed convincingly that chondroitin sulfate and dermatan sulfate formed hybrids. The explanation turned out to be a partial modification of uronic acid residues at the polymer level (epimerization) which turned chondroitin sulfate into dermatan sulfate. The original discovery of hybrids was the start of a whole field of studies of the modifications at the polymer level, which turned out to be the basis for the formation of specific sequences, e.g. in heparin. Such sequences are important for many of the specific biological functions of the polysaccharides (e.g. anticoagulant activity of heparin).

Lennart Rodén and collaborators have subsequently performed important work on the epimerization as well as on the chain initiation by xylosyltransferase and other enzymatic reactions which take part in the synthesis and degradation of polysaccharides. His bibliography lists more than 200 papers and his co-authors come from all over the world.

A characteristic of the work of Lennart Rodén is perfectionism. Today the development of the biological sciences is moving so fast that many investigators neglect the basic experiments required for a rigorous treatment of a problem. Lennart has never waived on this point, which makes him unique. It may take years to finish a paper but when it is written it is clear and the conclusions are undeniable.

Perhaps the most significant of Lennart's contributions has been his work as a teacher. He has been the scientific father of a generation of brilliant biochemists. His pupils have carried on the work he started to a great sophistication and as a result important biological principles have been revealed which also have had important clinical implications. Lennart would be the first to point out that the accomplishments of his laboratory are due, in no small measure, to the hard work and stimulating presence of his younger colleagues, and he treasures the lifelong friendships that have developed as a byproduct of the experiments at the lab bench.

Even a short biographical sketch of Lennart Rodén must include Kajsa, his wife of 45 years. Lennart and Kajsa have always been very close. They have four children. Eighteen years ago Kajsa suffered a stroke and no one except Lennart thought that she would survive. Lennart was right, but now she is confined to a wheelchair. Since 1977 they have always been together so that Lennart can help Kajsa whenever needed. She goes with him to work and on his travels and she helps him with the office work. To all their friends and admirers Kajsa and Lennart are inseparable and our tribute to Lennart is also a tribute to Kajsa. The members of the Glycosaminoglycan Community wish Kajsa and Lennart many happy returns.

Torvard Laurent

MEETING REPORT

In excess of 100 friends and colleagues of Lennart Rodén gathered in Birmingham, Alabama on November 13 and 14, 1994, to celebrate Lennart's 65th birthday. Highlights of Lennart's research career and many of the unusual and amusing incidents which dotted that career were recounted informally by speakers at a reception and dinner held on Sunday evening, 13 November.

The main event was a symposium entitled: *Glycosaminoglycans and Connective Tissue during the Rodénian Era.* **Torvard Laurent** gave a brief welcoming address. With rare exception, the speakers who followed were ex-students or folks who had sometime during the past 30 years collaborated with Lennart Rodén. There were some constant themes in the symposium talks: recognition that Lennart's research findings have withstood the test of time, and that he has encouraged and been generous with good advice to so many. Above all, there were the expressions of affection for Lennart and Kajsa.

The opening session dealt with **'Structures of Glycosaminoglycans and Proteoglycans.' Vincent Hascall**, sporting only half of a tie (being of silk, part had been donated to the Rodén lab for use as xylosyltransferase acceptor), spoke on 'Chondroitin sulfate revisited.' He recounted Lennart Rodén's pioneering studies on the structure and biosynthesis of the linkage region of chondroitin sulfate, and more recent work on the structure of the nonreducing ends of chains. **Tatsuya Yamagata** described a new zymographic method for the detection of glycosaminoglycan-degrading activities. He reported the very interesting finding of distinct hyaluronan- and hyaluronan/chondroitin sulfate-degrading activities, which were detected at an acidic pH in serum. **Anders Hjerpe** spoke on 'Sequencing of dermatan sulfate with the use of lyases and ion-pair HPLC.' His newly-reported HPLC methods can resolve the 23 different disaccharides which may be released by lyase digestion of dermatan sulfate. The structural analysis of dermatan sulfate chains from pig skin using such methods was described. That dermatan sulfate structure is very diverse, but regulated, was emphasized. **Birgitta Lindahl**, who was a student in Lennart Rodén's laboratory in the 1960s, described her recent studies of the heparan sulfate component of brain amyloid of Alzheimer patients. This heparan sulfate appears to have a higher content of N-sulfated groups than that found in normal brain. **John Couchman** reviewed the structure of perlecan, its ubiquity in basement membranes and its interactions, especially with FGF. The evidence for alternatively spliced forms of the perlecan core protein and the question of dermatan sulfate attachment sites were addressed. **Dick Heinegård** reviewed the growing list of small proteoglycans which possess leucine-rich repeats. Such protein cores serve a number of different, specific binding functions e.g. of chondroadherin to chondrocyte cell surface $\alpha_2\beta_1$ integrin, and decorin to collagen. Of particular interest was the report of type II collagen binding through a subclass of dermatan

Figure 2(a) & (b). Glycosaminoglycans and connective tissue during the Rodénian era. A symposium in honour of Professor Lennart Rodén held in Birmingham, Alabama, November 13–14, 1994.

Photography Identification: 1. Gerard Armand; 2. Peter Neame; 3. Harry Schachter; 4. Tatsuya Yamagata; 5. Batia Feingold: 6. John Jensen; 7. Robert Wells; 8. Martin Matthews; 9. Elias Meezan; 10. James Pittman; 11. Bigitta Lindahl; 12. Kajsa Rodén; 13. Lennart Rodén; 14. Elizabeth Neufeld; 15. Jerry Thompson; 16. Dick Heinegard; 17. Richard Mayne; 18. David Feingold; 19. Bruce Caterson; 20. Shastin Gardell; 21. B. Radhakrishnamurthy; 22. Erwin Coyne; 23. Torvard Laurent; 24. Vincent Hascall; 25. Ulf Lindahl; 26. Harry Bostrom; 27. Kristofer Rubin; 28. Lena Kjellen; 29. Alva Kjellen; 30. Steffan Johansson; 31. Erland Kjellen; 32. Sven Gardell; 33. John Schutzbach; 34. Ulla Laurent; 35. John Scott; 36. Rama Krishna; 37. Jin-Ping Li; 38. Christiane Sepulchre; 39. Anne Vezza; 40. John Baker; 41. Richard Reynertson; 42. Magnus Höök; 43. Hans Kresse; 44. Anders Malmstrom; 45. Marianne Malmstrom; 46. Ed Conrad; 47. Edward Dalferes.

sulfate chains of decorin. The interaction appears to be important in restraining the swelling of cartilage. **Peter Neame** discussed the relatedness of leucine-rich proteins with particular attention given to chondroadherin. This session concluded with a talk by **Richard Mayne** on 'Type IX: a collagen or proteoglycan?' He discussed his own interesting studies on the role of the unusually long chondroitin sulfate chain of type IX collagen in maintaining a properly dispersed network of collagen fibrils in the chicken vitreous: a role which is assigned to hyaluronan in vitreous of the mammalian eye.

Session 2 of the Symposium was titled '**Biosynthesis of Polysaccharides.**' In the first talk, **David Feingold** spoke on 'UDP-glucose dehydrogenase: a key player in heparin biosynthesis.' **Ulf Lindahl** reviewed the structural features of heparin and heparan sulfate chains which are needed for binding antithrombin, FGF-2 and the FGF-2 receptor. Ulf also discussed the sequence of biosynthetic events that could lead to the synthesis of the specific protein-binding features of these glycosaminoglycan chains. New evidence was presented for the natural occurrence of free amino groups within some heparan sulfate chains. **Lena Kjellén** compared the properties of the N-deacetylase/N-sulfotransferase from mouse mastocytoma with that from rat liver (reported by Carlos Hirschberg). They show some differences and are the products of two different genes. Although the further and later O-sulfation of the heparan sulfate/heparin chain is largely determined by the activity of this dual-activity enzyme, the two different reported enzymes are not separately responsible for heparin and heparan sulfate synthesis, respectively. Continuing the theme of heparan sulfate/heparin biosynthesis, **Jin-Ping Li** described her work on the successful purification and molecular cloning of the glucuronosyl 5-epimerase from bovine liver. **Anders Malmström** discussed his own studies of the factors which affect the activity of the glucuronosyl 5-epimerase involved in dermatan sulfate synthesis. *In vitro*, addition of TGF-ß and stimulating 4-sulfation of the growing chain were found to decrease and increase, respectively, the proportion of iduronic acid residues in the synthesized dermatan sulfate. **John Schutzbach** briefly reminisced about his postdoctoral work at La Rabida and described his recent studies on the molecular properties of the dolichol-P-mannose synthase.

The final session of the day was on '**The Linkage Region.**' In deference to Lennart, **Jeff Esko's** talk was titled 'It all starts with Xylose.' The emphasis of his talk was on the α-*N*-acetylglucosaminyltransferase (α-GlcNAc-T1), which is responsible for the addition of the first GlcNAc to the linkage region. The activity of this enzyme appears to determine that the glycosaminoglycan synthesized is heparan sulfate, not chondroitin sulfate. **Nancy Schwartz** discussed the substrate specificity of xylosyltransferase and recent evidence concerning the subcellular location for its action. Present evidence favours activity in the late ER and transitional Golgi. Regrettably, **Lars-Åke Fransson** was unable to attend due to family bereavement. His position in the symposium program was ably filled by **Tracy Curenton,** a current student in Lennart Rodén's laboratory. She presented data which shows that glucuronyl transfer in the synthesis of glycoprotein-linked HNK-1 and the linkage region of chondroitin sulfate is supported by two distinct glucuronosyltransferases. **Christiane Sepulchre** reported a very thorough study of various thio-ß-xylopyranosides as acceptors in the assay of galactosyltransferase I. 5-Thio-ß-xylopyranosides were shown to be excellent substrates for the enzyme from cartilage, liver and aorta. In the final talk of the session, **Eli Meezan** showed that the endogenous acceptor of xylose, which is present in crude preparations of xylosyltransferase from embryonic chick cartilage, is glycogenin. Glycogenin can autocatalyse the addition of xylose or glucose from the corresponding UDP derivatives.

Martin B. Mathews, the Nestor of connective tissue biology, opened session 4 (**'Functional Aspects of Connective Tissue'**) and gave of his wisdom and insight in a presentation entitled 'A vision of connective tissue.' Responding first to an introductory remark by Magnus Höök about the importance of the initial B in his name, he said that it signified four words starting with the letter b – be, becoming, behaving, and believing ('I believe there is money in the bank.'). The universal need for connective tissues in various life forms and Nature's different solutions to this requirement were illustrated by a picture of the highly organized sheets of cellulose fibres in algae and the aligned collagen fibres in frog skin. It was pointed out that we still know very little about the developmental processes that lead to the formation of the supramolecular architecture exemplified by the two tissues. In addition to the distinct genetic forces of evolution, an environmental plasticity, which may or may not be genetically determined, also influences the individual's ability to survive in a new milieu. Martin noted that Kajsa and Lennart apparently possessed this quality since they had adapted well to living in Birmingham. He concluded his presentation with a recital of the poem 'The man with the blue guitar' (1937) by Wallace Stevens. Awesome! Go read it yourself!

John E. Scott celebrated his 64th birthday on the second day of the meeting and spoke on 'Supramolecular organization and molecular recognition in extracellular matrix.' Based on the premise that the three-dimensional structure of the glycosaminoglycans determines, in large part, their behaviour in the extracellular matrix, Scott has sought to simplify our view of these molecules by focusing attention on the carbohydrate backbone and ignoring, as a first approximation, the substituent carboxylate, 2-acetamido, and sulfate groups. Viewed from this perspective, the glycosaminoglycans fall into three classes: (1) polymaltoses (heparin and heparan sulfates); (2) polylactoses (keratan sulfates and chondroitin sulfates); and (3) polycellobiose (hyaluronan). From NMR data gathered over more than a decade by Scott and his collaborators, it has been concluded that all extracellular matrix glycosaminoglycans exist in solution as two-fold helices. Molecular modelling of hyaluronan has shown the presence of regularly arranged hydrophobic patches spanning over three monosac-

charide units, and these hydrophobic areas provide the structural basis for interactions between hyaluronan and hydrophobic molecules as well as between the hyaluronan molecules themselves. The modifying effects of the substituents on the interactions of the glycosaminoglycans with other extracellular matrix molecules were also discussed, with particular emphasis on the importance of the position of the sulfate groups of the galactosaminoglycans for the organization of collagen fibrils in the tissues. Throughout his presentation, Scott showed that he was fully aware of the Einstein caveat: 'Things should be made as simple as possible, but not any simpler.'

Hans Kresse succinctly presented his interesting work on the growth factor activity of an osteosarcoma-derived chondroitin sulfate proteoglycan (PG-100). Although the proteoglycan itself displayed this property, its activity was substantially enhanced by the removal of the polysaccharide chains and approached that of CSF-1 (colony stimulating factor 1). Amino acid sequencing indicated that the core protein of PG-100 was similar to CSF-1, and partial cDNA sequencing has so far shown complete identity of the sequenced portion with the corresponding segment in CSF-1. It was suggested on the basis of the respective survival times in collagen gels that PG-100 represents a stable storage form of CSF-1 or a similar substance.

Anne Woods addressed the role of cell surface heparan sulfate proteoglycans as signalling molecules in cell adhesion. On the basis of experiments with peptides representing different domains in the fibronectin molecule, it was proposed that focal adhesion formation in response to fibronectin involves two processes. The cell-binding domain (RGD sequence) interacts with integrins in response to a signal involving phosphorylation by attendant tyrosine kinases. Second, a heparin-binding domain (PRARI) interacts with a cell surface heparan sulfate proteoglycan as a consequence of activation of protein kinase C. Details of these interactions are under continuing investigation.

Staffan Johansson described the ligand-binding properties of a recently discovered member of the integrin family, $\alpha_9\beta_1$. The new integrin was isolated from rat liver by affinity chromatography on Sepharose conjugated with the peptide GRGDSPC. The cysteine residue in this peptide was essential for binding. In some contrast, replacement of arginine and/or aspartic acid with lysine and glutamic acid, respectively, weakened but did not abolish the interaction. Interactions with EHS-laminin and collagen type I were also described.

Session 5 was concerned with '**Pathological Aspects of Connective Tissue**' and was opened by **Robert Morris**, who spoke about the problem of frequent scar formation following various forms of eye surgery and expressed hope that this complication would eventually be eliminated by continued research in the connective tissue area. He also pointed out that the Helen Keller Eye Research Foundation had been started on the initiative of Magnus Höök, who was a member of Rodén's connective tissue research group at the time.

Torvard Laurent gave a presentation entitled 'News and views on hyaluronan.' He chronicled briefly the earlier studies on hyaluronan catabolism, including the important discovery that circulating hyaluronan is taken up and degraded primarily by the sinusoidal endothelial cells of the liver. Recent work on the isolation and characterization of the hyaluronan receptor in the endothelial cells was described, and the properties of this receptor were compared with those of other hyaluronan-binding proteins such as ICAM-1 and CD 44. The roles of these proteins in inflammation and malignancy were discussed.

David Pritchard presented an interesting study of the neuraminidase of group B streptococci which, as it turned out, was not neuraminidase at all. The enzyme was assayed routinely with the colorimetric thiobarbituric acid method, but at one point in the investigation, it became necessary to carry out a more complete characterization of the reaction product. (This age-old stratagem was also applied successfully by Saul Roseman to the product of another enzymatic reaction in his original elucidation of the structure of *N*-acetylneuraminic acid.) Surprisingly, it was discovered that the product was the unsaturated disaccharide from hyaluronan (also reacting positively in the thiobarbituric acid assay), and it was therefore concluded that the neuraminidase was actually a hyaluronidase. The hyaluronan substrate was found to be present as an impurity in the mucin preparation used as a substrate for the neuraminidase. Further studies of the reaction mechanism and cloning of the hyaluronidase were also reported.

Elizabeth F. Neufeld gave a lucid exposé of the molecular genetics of the α-L-iduronidase deficiency diseases and approaches to treatment. She discussed the paradoxical situation that patients with the Hurler-Scheie syndrome are much less severely afflicted than the typical Hurler patients, although they have no detectable α -L- iduronidase, as determined by standard assay methodology. The explanation seems to be that the Hurler-Scheie patients do indeed produce a small amount of normal enzyme (<1% of the amount in normal controls), and this low activity apparently alleviates partially the defect in glycosaminoglycan degradation. Therapeutic approaches were also discussed (bone marrow transplantation, enzyme replacement therapy, and gene therapy), and progress in enzyme replacement treatment of dogs afflicted with the Hurler syndrome was reported. Attempts at gene therapy have not yet been successful.

In what he characterized as a 90 mph talk (and it was obvious that he has not slowed down in his old age), **Bruce Caterson** described the structural alterations in proteoglycans in arthritis and the metabolic changes that occur in diseases of the arthritis group. He also described recent approaches to new drug therapy.

Kevin McCarthy presented his studies of proteoglycans in relation to glomerulosclerosis, with emphasis on the disparity between the distributions of heparan sulfate proteoglycan and chondroitin sulfate proteoglycan (bamacan). Whereas the

former is found in both the glomerulus and the mesangial cell area, bamacan is found exclusively in the mesangial cell region. The changes resulting from diabetes (hyperglycaemia) were also described as they referred to the metabolism of the two proteoglycans.

Kristofer Rubin described a series of interesting experiments addressing the regulation of fluid balance in the extracellular matrix and, in particular, the role of interactions between cells and fibrous elements in the control of oedema. With an experimental system consisting of fibroblasts growing in collagen gels in a multiwell plastic plate, the effects of a number of substances were tested by observing the gel size after a standardized incubation time. It was found that PDGF-BB was especially effective in promoting contraction of the gels, and it was further demonstrated that cell surface integrins (mainly $\alpha_2\beta_1$) were participants in this process, as indicated by the inhibition of shrinkage caused by the appropriate antibodies. Analogous effects on the interstitial fluid pressure were observed in *in vivo* experiments upon administration of integrin antibodies and PDGF-BB.

J. Robert E. Fraser has pioneered investigations of the catabolism of hyaluronan and has established, together with Torvard and Ulla Laurent and their collaborators, that the polysaccharide is degraded *in vivo* in three different locations: (1) in the tissue where it has been synthesized; (2) in the sinusoidal endothelial cells of the liver (and to some extent also in the Kupffer cells); and (3) in the lymph nodes. Fraser's presentation was focused on the third locus, and impressive and technically advanced experiments were described, in which the concentrations and properties of hyaluronan had been measured in afferent and efferent lymph vessels. It was concluded that a substantial proportion of the hyaluronan in lymph is degraded upon passage through the lymph nodes.

Gerald Hart, opening session 6 ('**Glycoproteins**'), gave an overview of the glycosylation of nuclear and cytoplasmic proteins by transfer of single *N*-acetylglucosamine residues to serine and threonine units in the proteins. It is now apparent that there is a wealth of proteins that undergo reversible glycosylation of this type. Among the glycosylated proteins are RNA polymerase II and transcription factors involved in protein biosynthesis. The finding that the sugar residues may turn over 50 times faster than the protein itself points to an important regulatory function, and this assumption is further supported by the observation that the same sites in a protein may be either glycosylated or phosphorylated.

Harry Schachter, after heaping appropriate insults on Lennart, gave a stimulating talk about a recently discovered disease, named carbohydrate-deficient glycoprotein (CDG) syndrome type II, which results from a deficiency in glycoprotein biosynthesis. Presently, two patients with the disease are known, a boy in Belgium and a girl in Iran. Both are suffering from severe psychomotor retardation. The nature of the defect was indicated by determination of the isoform pattern of serum transferrin and structural analysis of disialotransferrin, which constituted the major fraction. In each molecule, two truncated monoantennary oligosaccharides were found, consisting of Asn-linked sialyl-Gal-GlcNAc-Man(α1→3)[Man(α1 → 6)]Man(β1 → 4)GlcNAc(β1 → 4)GlcNAc. This structure suggested a deficiency in the medial-Golgi enzyme, *N*-acetylglucosaminyltransferase II. Direct assays of fibroblast extracts (carried out by Schachter himself and, to be on the safe side, also by a student) demonstrated a profound deficiency in this enzyme. The primary structure of the defective enzyme is presently under investigation. Together with studies on CDG syndrome type I, of which more than 100 cases are known, these investigations clearly illustrate the importance of N-linked oligosaccharides for the normal development and function of the nervous system.

For more than a decade, **John and Lisa Fessler** have devoted their research efforts to the study of the extracellular matrix proteins synthesized by Drosophila haemocytes in culture. Many proteins have been isolated and compared with their counterparts in vertebrates, if such exist. Recently, a protein of unknown function was isolated and sequenced, which turned out to be a glucosyltransferase catalysing transfer from UDP-glucose to a mannose residues in Man_9-GlcNAc-GlcNAc-proteins that were malfolded. An enzyme with similar specificity has previously been found by Parodi in the endoplasmic reticulum of vertebrate liver cells. Substrates recognized by the Drosophila enzyme were, e.g. the Drosophila proteins laminin, peroxidasin, and glutactin, and denatured (but not native) bovine thyroglobulin. The possible role of the glucosyltransferase in the processing of malfolded proteins in the endoplasmic reticulum was discussed.

Concluding this session, **Dan Urry** spoke about the ΔT_t hydrophobic perspective of protein folding and function and presented an exciting video, which illustrated dramatically the conversion of 'chemical' to mechanical energy, as it applied to elastin-like polymers.

Lennart Rodén concluded the symposium by extending his warm thanks to the organizers (Torvard Laurent and Ulf Lindahl in Uppsala and John Baker and Jerry Thompson in Birmingham) and to the participants who had come from near and far to share their knowledge in what seemed to be a valiant attempt to give him some basic education in the area of research that he has now pursued for several decades.

John Baker, with considerable assistance from **Lennart Rodén**