When the Inner Ear Biochemistry Workshop started in 1964, we knew of giants who had given us some the key ideas. They included

Alfonso Corti

Robert Barany

Georg von Bekesy

Halliwell Davis

and many others……

What science had happened be fore the workshop started?

Elsewhere we had seen the birth of molecular biology

No. 4356 April 25, 1953 NATURE 737

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

WE wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey[1]. They kindly made their manuscript available to us in advance of publication. Their model consists of three inter-twined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion, this structure is unsatisfactory for two reasons: (1) We believe that the material which gives the X-ray diagrams is the salt, not the free acid. Without the acidic hydrogen atoms it is not clear what forces would hold the structure together, especially as the negatively charged phosphates near the axis will repel each other. (2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has also been suggested by Fraser (in the press). In his model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for this reason we shall not comment on it.

We wish to put forward a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram). We have made the usual chemical assumptions, namely, that each chain consists of phosphate diester groups joining ß-D-deoxy-ribofuranose residues with 3',5' linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow righthanded helices, but owing to the dyad the sequences of the atoms in the two chains run in opposite directions. Each chain loosely resembles Furberg's[2] model No. 1; that is, the bases are on the inside of the helix and the phosphates on the outside. The configuration of the sugar and the atoms near it is close to Furberg's 'standard configuration', the sugar being roughly perpendicular to the attached base. There is a residue on each chain every 3·4 A. in the z-direction. We have assumed an angle of 36° between adjacent residues in the same chain, so that the structure repeats after 10 residues on each chain, that is, after 34 A. The distance of a phosphorus atom from the fibre axis is 10 A. As the phosphates are on the outside, cations have easy access to them.

The structure is an open one, and its water content is rather high. At lower water contents we would expect the bases to tilt so that the structure could become more compact.

The novel feature of the structure is the manner in which the two chains are held together by the purine and pyrimidine bases. The planes of the bases are perpendicular to the fibre axis. They are joined together in pairs, a single base from one chain being hydrogen-bonded to a single base from the other chain, so that the two lie side by side with identical z-co-ordinates. One of the pair must be a purine and the other a pyrimidine for bonding to occur. The hydrogen bonds are made as follows: purine position 1 to pyrimidine position 1; purine position 6 to pyrimidine position 6.

If it is assumed that the bases only occur in the structure in the most plausible tautomeric forms (that is, with the keto rather than the enol configurations) it is found that only specific pairs of bases can bond together. These pairs are: adenine (purine) with thymine (pyrimidine), and guanine (purine) with cytosine (pyrimidine).

In other words, if an adenine forms one member of a pair, on either chain, then on these assumptions the other member must be thymine; similarly for guanine and cytosine. The sequence of bases on a single chain does not appear to be restricted in any way. However, if only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain is given, then the sequence on the other chain is automatically determined.

It has been found experimentally[3,4] that the ratio of the amounts of adenine to thymine, and the ratio of guanine to cytosine, are always very close to unity for deoxyribose nucleic acid.

It is probably impossible to build this structure with a ribose sugar in place of the deoxyribose, as the extra oxygen atom would make too close a van der Waals contact.

The previously published X-ray data[5,6] on deoxyribose nucleic acid are insufficient for a rigorous test of our structure. So far as we can tell, it is roughly compatible with the experimental data, but it must be regarded as unproved until it has been checked against more exact results. Some of these are given in the following communications. We were not aware of the details of the results presented there when we devised our structure, which rests mainly though not entirely on published experimental data [illegible]

It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

[illegible] in building it, together with a set of co-ordinates for the atoms, will be published elsewhere.

We are much indebted to Dr. Jerry Donohue for constant advice and criticism, especially on interatomic distances. We have also been stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Dr. M. H. F. Wilkins, Dr. R. E. Franklin and their co-workers at King's College, London. One of us (J.D.W.) has been aided by a fellowship from the National Foundation for Infantile Paralysis.

J.D. WATSON
F.H. C. CRICK

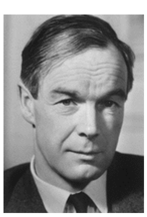
Medical Research Council Unit for the Study of the Molecular Structure of Biological Systems, Cavendish Laboratory, Cambridge. April 2.

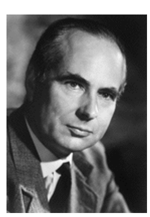
1 Pauling, L., and Corey, R. B., Nature, 171, 346 (1953); Proc. U.S. Nat. Acad. Sci., 39, 84 (1953).
2 Furberg, S., Acta Chem. Scand., 6, 634 (1952).
3 Chargaff, E., for references see Zamenhof, S., Brawerman, G., and Chargaff, E., Biochim. et Biophys. Acta, 9, 402 (1952).
4 Wyatt, G.R., J. Gen. Physiol., 36, 201 (1952).
5 Astbury, W.T., Symp. Soc. Exp. Biol. 1, Nucleic Acid, 66 (Camb. Univ. Press, 1947).
6 Wilkins, M. H. F. and Randall, J. T. Biochim. et Biophys. Acta, 10, 192 (1953).

This figure is purely diagrammatic. The two ribbons symbolize the two phosphate—sugar chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis

"It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying method for the genetic material."

Elsewhere: we had seen the birth of cellular biophysics





Alan Hodgkin and Andrew Huxley

J. Physiol 1952

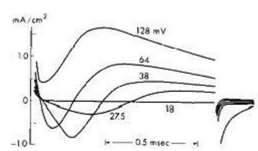
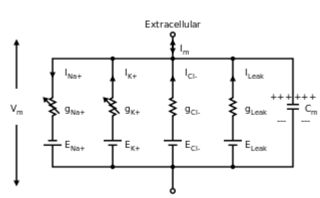
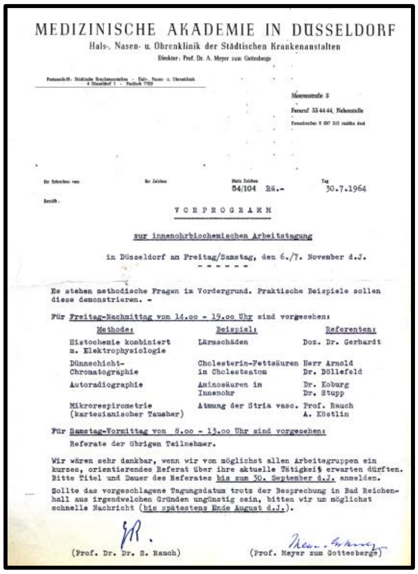


Fig. 3:16. Squid axon membrane current densities after changes of potential from the resting potential as shown.



As Jochen Schacht describes, Sigurd Rauch convened the first workshop to enable a research interface between clinicians and biochemists:



MEDIZINISCHE AKADEMIE IN DÜSSELDORF
Hals-, Nasen- u. Ohrenklinik der Städtischen Krankenanstalten
Direktor: Prof. Dr. A. Meyer zum Gottesberge

Moorenstraße 5
Fernruf 35 44 44, Nebenstelle

Mein Zeichen 54/104 Rä.- Tag 30.7.1964

VORPROGRAMM

zur innenohrbiochemischen Arbeitstagung

in Düsseldorf am Freitag/Samstag, den 6./7. November d.J.

Es stehen methodische Fragen im Vordergrund. Praktische Beispiele sollen diese demonstrieren. -

Für Freitag-Nachmittag von 14.oo - 19.oo Uhr sind vorgesehen:

Methode:	Beispiel:	Referenten:
Histochemie kombiniert m. Elektrophysiologie	Lärmschäden	Doz. Dr. Gerhardt
Dünnschicht-Chromatographie	Cholesterin-Fettsäuren im Cholesteatom	Herr Arnold Dr. Döllefeld
Autoradiographie	Aminosäuren im Innenohr	Dr. Koburg Dr. Stupp
Mikrorespirometrie (kartesianischer Taucher)	Atmung der Stria vasc.	Prof. Rauch A. Köstlin

Für Samstag-Vormittag von 8.oo - 13.oo Uhr sind vorgesehen:
Referate der übrigen Teilnehmer.

Wir wären sehr dankbar, wenn wir von möglichst allen Arbeitsgruppen ein kurzes, orientierendes Referat über ihre aktuelle Tätigkeit erwarten dürften. Bitte Titel und Dauer des Referates bis zum 30. September d.J. anmelden.

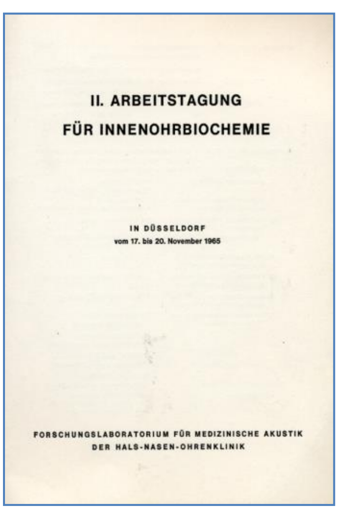
Sollte das vorgeschlagene Tagungsdatum trotz der Besprechung in Bad Reichenhall aus irgendwelchen Gründen ungünstig sein, bitten wir um möglichst schnelle Nachricht (bis spätestens Ende August d.J.).

(Prof. Dr. Dr. S. Rauch) (Prof. Meyer zum Gottesberge)

Sigurd Rauch

Invitation: 1st Workshop November 6 & 7, 1964

To be followed in 1965 by a 2nd Workshop on Inner Ear Biochemistry



II. ARBEITSTAGUNG
FÜR INNENOHRBIOCHEMIE

IN DÜSSELDORF
vom 17. bis 20. November 1965

FORSCHUNGSLABORATORIUM FÜR MEDIZINISCHE AKUSTIK
DER HALS-NASEN-OHRENKLINIK

Topics

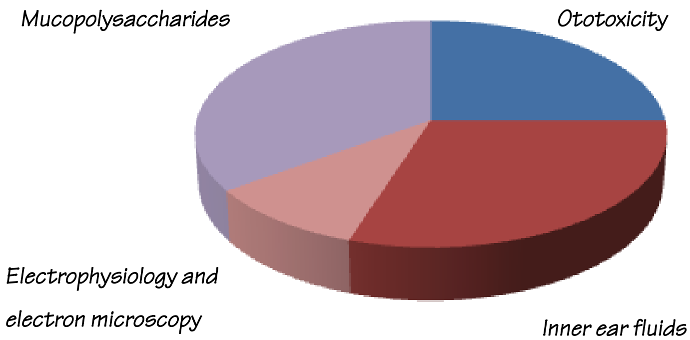
Mucopolysaccharides in the inner ear

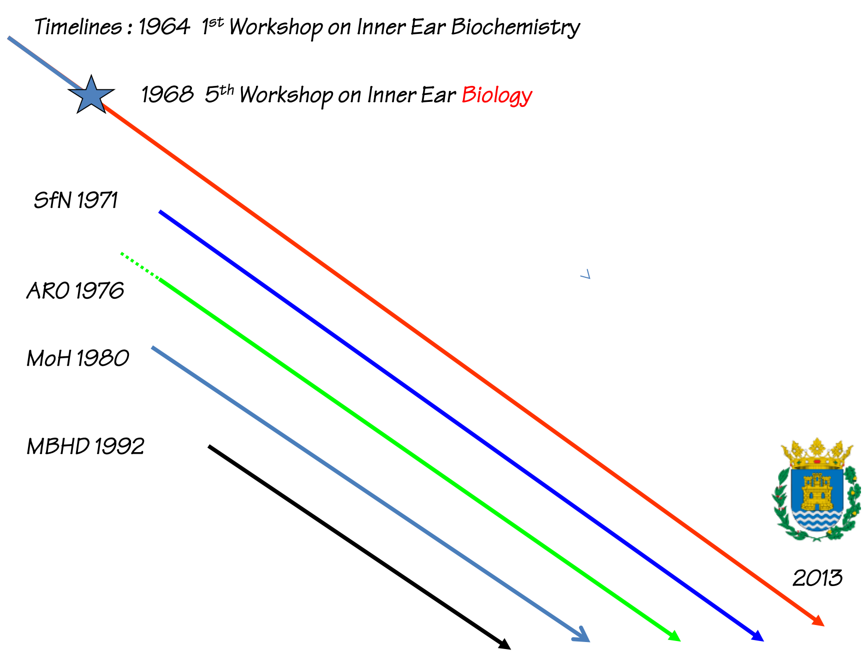
Inner ear fluids:
composition, secretion and absorption

Membrane problems :
electron microscopy and electrophysiology

Ototoxicity:
pharmacology and pathology

How the 1965 discussions were divided up





How has inner ear biology developed?
Here are (some!) enabling technologies

1950s -	Electron microscopy
1960s -	Recording from nerves and cells
	(1976 – low noise patch clamp)
1965	Fluorescence microscopy
1972	Monoclonal antibodies
1989	GFP and other probes
Early 1980s	Commercial confocal microscopes
	(2002 - commercial multiphoton microscopes)
1980s	Interferometric position sensors

And now? Molecular biology kits + Sequencing facilities + ….PCs

The 1960s and '70s : What was happening?

1962 Electron microscopy of the cochlea (Engstrom, Wersall, Flock)

1965 Recording from auditory nerve (Kiang / Rose)

1969 Mechanics: resonance of the basilar membrane? (Huxley)

1970s Nerve tracing methods (Spoendlin and others)

1973 Single hair cell microphonics (Flock)

1971 Tuning in the basilar membrane? (Rhode)

1974 Ototoxic damage to outer hair cells (Dallos)

1977 Contractile proteins in stereocilia! (Flock)

1964 1st Workshop on Inner Ear Biochemistry

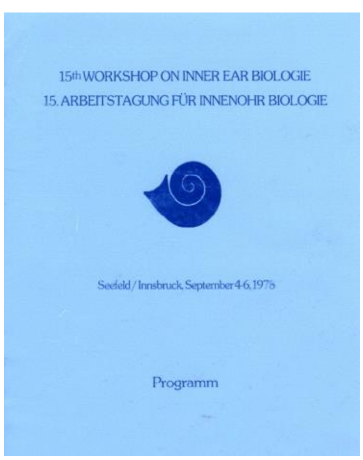
1968 5th Workshop on Inner Ear Biology

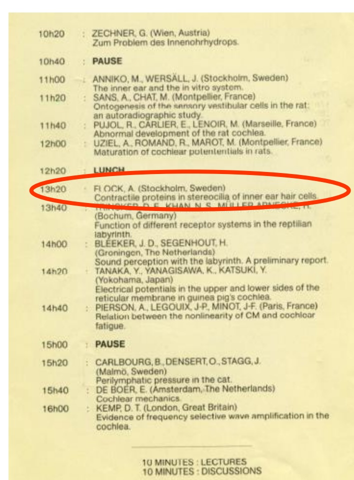
1978: Seefeld, Austria

Let's have a look at some of the early meetings:

50th Inner Ear Biology Workshop 2013

1978 : 15th Workshop on Inner Ear Biology



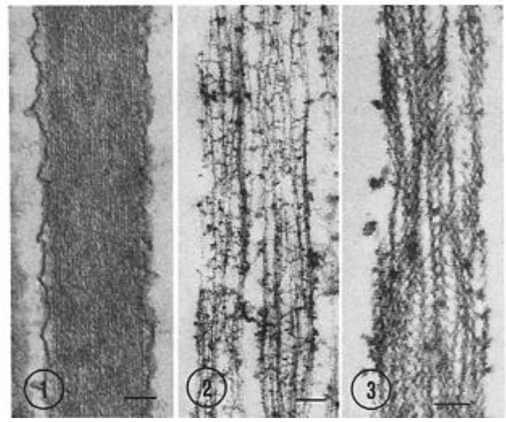


10h20	:	ZECHNER, G. (Wien, Austria) Zum Problem des Innenohrhydrops.
10h40	:	**PAUSE**
11h00	:	ANNIKO, M., WERSÄLL, J. (Stockholm, Sweden) The inner ear and the in vitro system.
11h20	:	SANS, A., CHAT, M. (Montpellier, France) Ontogenesis of the sensory vestibular cells in the rat: an autoradiographic study.
11h40	:	PUJOL, R., CARLIER, E., LENOIR, M. (Marseille, France) Abnormal development of the rat cochlea.
12h00	:	UZIEL, A., ROMAND, R., MAROT, M. (Montpellier, France) Maturation of cochlear potententials in rats.
12h20	:	**LUNCH**
13h20	:	FLOCK, A. (Stockholm, Sweden) Contractile proteins in stereocilia of inner ear hair cells.
13h40	:	[illegible] (Bochum, Germany) Function of different receptor systems in the reptilian labyrinth.
14h00	:	BLEEKER, J. D., SEGENHOUT, H. (Groningen, The Netherlands) Sound perception with the labyrinth. A preliminary report.
14h20	:	TANAKA, Y., YANAGISAWA, K., KATSUKI, Y. (Yokohama, Japan) Electrical potentials in the upper and lower sides of the reticular membrane in guinea pig's cochlea.
14h40	:	PIERSON, A., LEGOUIX, J-P., MINOT, J-F. (Paris, France) Relation between the nonlinearity of CM and cochlear fatigue.
15h00	:	**PAUSE**
15h20	:	CARLBOURG, B., DENSERT, O., STAGG, J. (Malmö, Sweden) Perilymphatic pressure in the cat.
15h40	:	DE BOER, E. (Amsterdam, The Netherlands) Cochlear mechanics.
16h00	:	KEMP, D. T. (London, Great Britain) Evidence of frequency selective wave amplification in the cochlea.

10 MINUTES : LECTURES
10 MINUTES : DISCUSSIONS

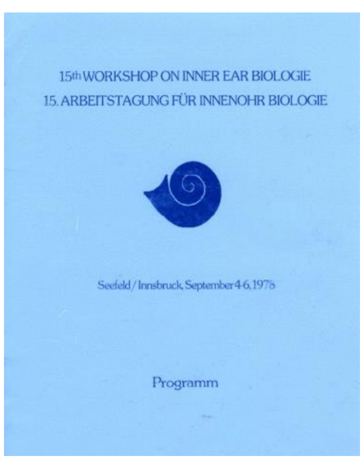
Seefeld, IEB 1978: Contractile proteins in hair cell stereocilia

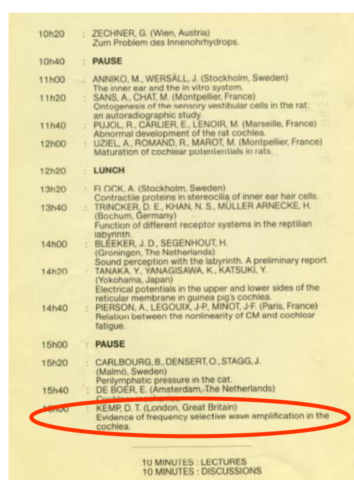
Ake Flock



Flock and Cheung, J Cell Biol 1977

1978 : 15th Workshop on Inner Ear Biology





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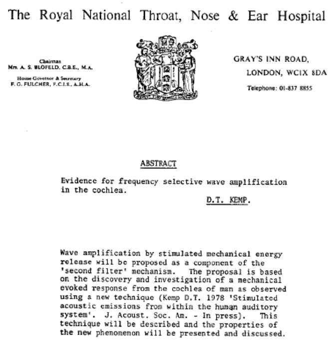
15h40	:	DE BOER, E. (Amsterdam, The Netherlands) [illegible]
16h00	:	KEMP, D. T. (London, Great Britain) Evidence of frequency selective wave amplification in the cochlea.

10 MINUTES : LECTURES
10 MINUTES : DISCUSSIONS

Seefeld IEB 1978: The 'Kemp Echo'



The Royal National Throat, Nose & Ear Hospital

Chairman
Mrs. A. S. BLOFELD, C.B.E., M.A.
House Governor & Secretary
F. G. FULCHER, F.C.I.S., A.H.A.

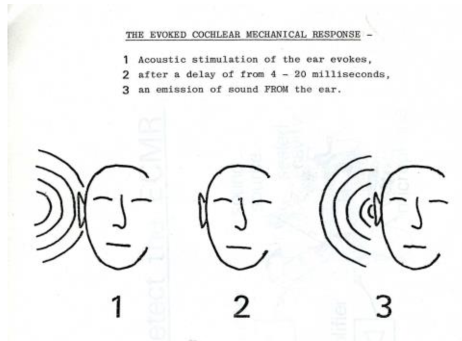
GRAY'S INN ROAD,
LONDON, WC1X 8DA
Telephone: 01-837 8855

ABSTRACT

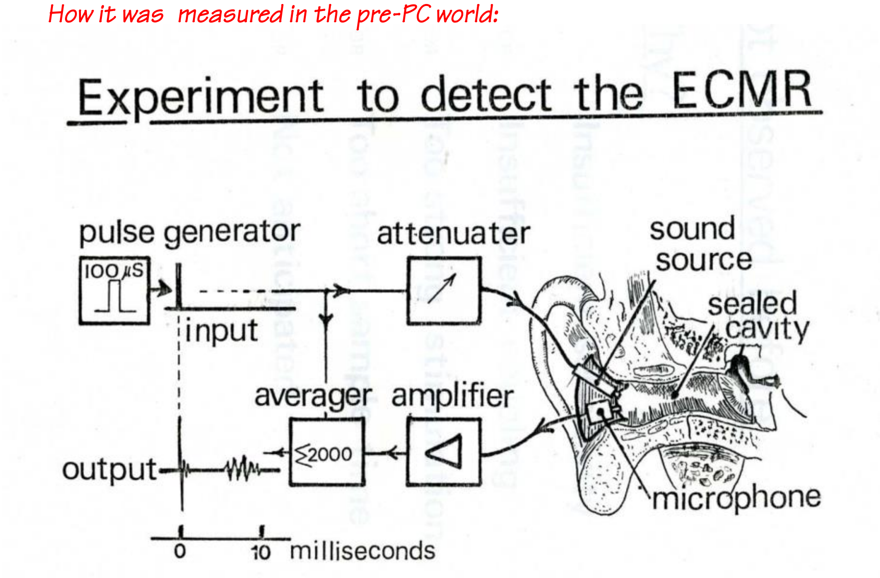
Evidence for frequency selective wave amplification in the cochlea.

D.T. KEMP.

Wave amplification by stimulated mechanical energy release will be proposed as a component of the 'second filter' mechanism. The proposal is based on the discovery and investigation of a mechanical evoked response from the cochlea of man as observed using a new technique (Kemp D.T. 1978 'Stimulated acoustic emissions from within the human auditory system'. J. Acoust. Soc. Am. - In press). This technique will be described and the properties of the new phenomenon will be presented and discussed.



How it was measured in the pre-PC world:



The 1980s: what was happening?

1976 Patch clamp recording methods (Neher & Sakmann)

1981 Embryonic Stems Cells (Martin Evans et al.):

1986 PCR (Mullis)

1976 – In vitro hair cell recording, frog (Hudspeth)

1979 – In vivo Intracellular IHCs (Russell & Sellick)

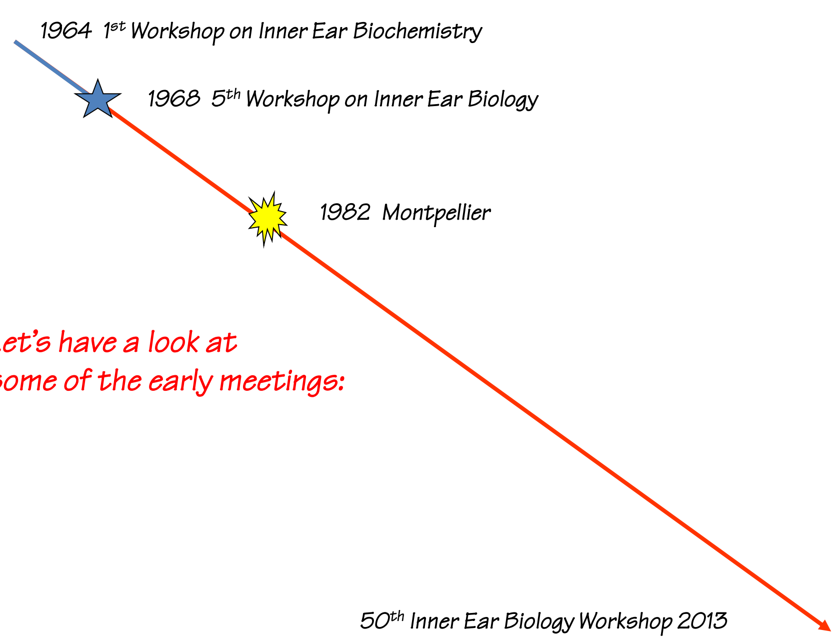
1982 - Recording from IHCs & OHCs (J.S-S & Dallos)

1981 - Electrical tuning in turtles (Crawford & Fettiplace)

1983 - Tip links (Pickles et al.)

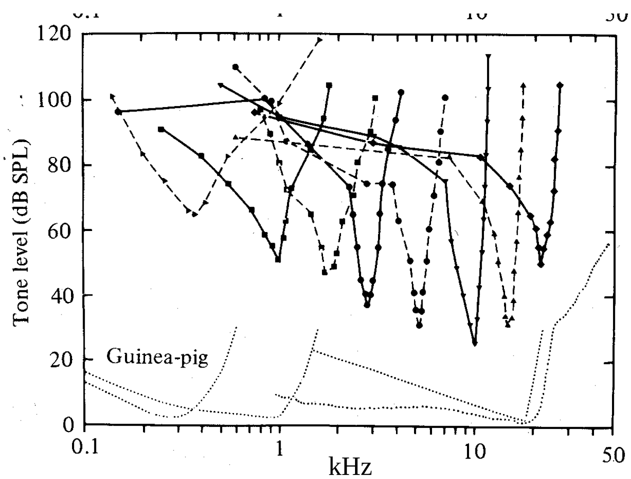
1984 - Outer hair cells are motile: Brownell et al

Cochlear implants: 1962 (House), 1978 (Clark)….



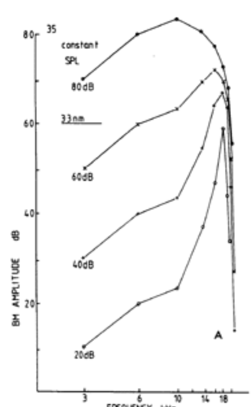
Let's have a look at
some of the early meetings:

The idea at the time was that auditory nerve fibres were tuned because there there was a 'second filter'. The physiological basis for the filter was unknown.



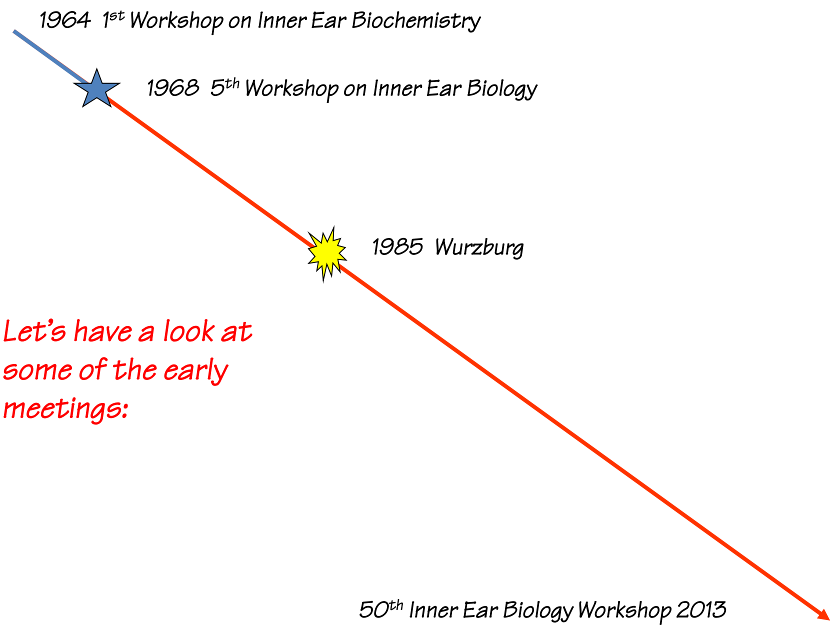
From Evans 1972 (cf Kiang in Cat 1965)

In 1982 it was announced that the basilar membrane itself is sharply tuned: first presented at IEB Montpellier on a single faxed poster!



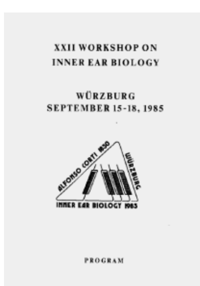
"We suggest that most of the frequency response and nonlinear behavior of inner hair cells and afferent fibers may be found in basilar motion".

Sellick, Patuzzi & Johnstone JASA 1982 (published after IEB)

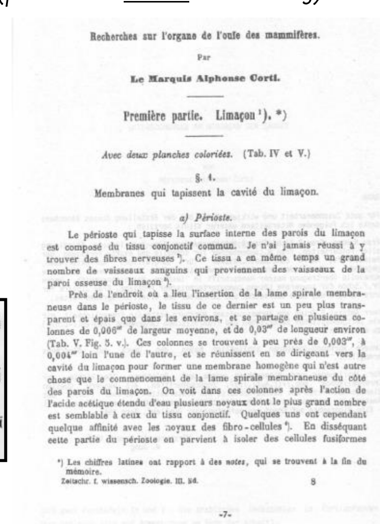


Let's have a look at some of the early meetings:

1985 : 22nd Workshop on Inner Ear Biology



135th anniversary of the doctoral thesis of Corti (published in French at Wurzburg).



Recherches sur l'organe de l'ouïe des mammifères.

Par

Le Marquis Alphonse Corti.

Première partie. Limaçon [1]). *)

Avec deux planches coloriées. (Tab. IV et V.)

§. 1.

Membranes qui tapissent la cavité du limaçon.

a) Périoste.

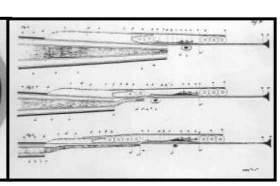
Le périoste qui tapisse la surface interne des parois du limaçon est composé du tissu conjonctif commun. Je n'ai jamais réussi à y trouver des fibres nerveuses [2]). Ce tissu a en même temps un grand nombre de vaisseaux sanguins qui proviennent des vaisseaux de la paroi osseuse du limaçon [3]).

Près de l'endroit où a lieu l'insertion de la lame spirale membraneuse dans le périoste, le tissu de ce dernier est un peu plus transparent et épais que dans les environs, et se partage en plusieurs colonnes de 0,006''' de largeur moyenne, et de 0,03''' de longueur environ (Tab. V. Fig. 5. v.). Ces colonnes se trouvent à peu près de 0,003''', à 0,004''' loin l'une de l'autre, et se réunissent en se dirigeant vers la cavité du limaçon pour former une membrane homogène qui n'est autre chose que le commencement de la lame spirale membraneuse du côté des parois du limaçon. On voit dans ces colonnes après l'action de l'acide acétique étendu d'eau plusieurs noyaux dont le plus grand nombre est semblable à ceux du tissu conjonctif. Quelques uns ont cependant quelque affinité avec les noyaux des fibro-cellules [4]). En disséquant cette partie du périoste on parvient à isoler des cellules fusiformes

*) Les chiffres latines ont rapport à des *notes*, qui se trouvent à la fin du mémoire.

Zeitschr. f. wissensch. Zoologie. III. Bd. 8

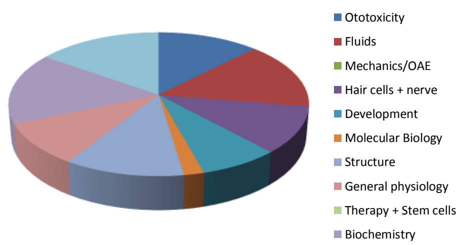
-7-



How had the range of topics exapanded by IEB 22 ?

Here are some session topics:

Development
Morphology
Cell Biology
Ototoxicity
Hair cell recording and cochlear mechanics
General physiology and electrophysiology
Biochemistry – immunology, neuropeptides, collagens



The 1990s and beyond: What was happening?

1989 Hair cell transcription factors, BRN3c/POUF43 (Ryan et al.)

1993 Hair cell regeneration (Forge et al; Warchol et al.)

1995 First deafness gene Myo7a   (Steel et al.)

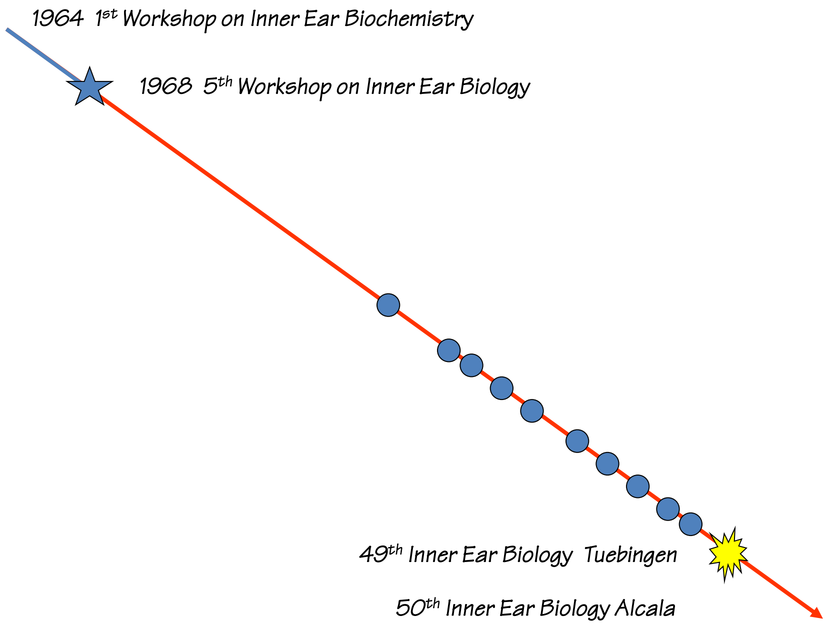
1997 Connexins (GJB2) (Kelsell et al.)

2000   Prestin (Zheng et al.)

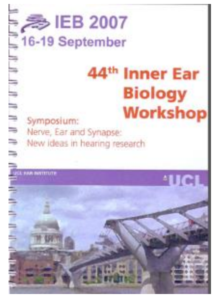
2002 -   Ribbon synapse structure and function

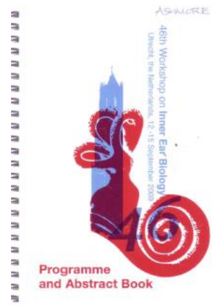
2005 -   Cochlear supporting cell - hair cell conversion..

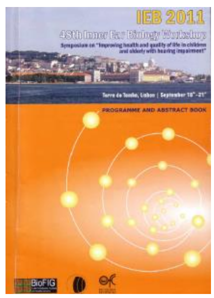
Stem cells… (wait!)

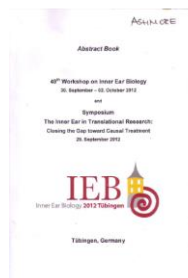


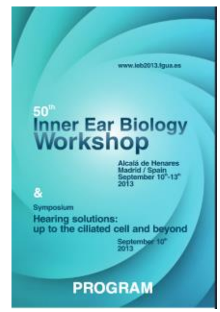
Abstract and programme covers become more colourful....



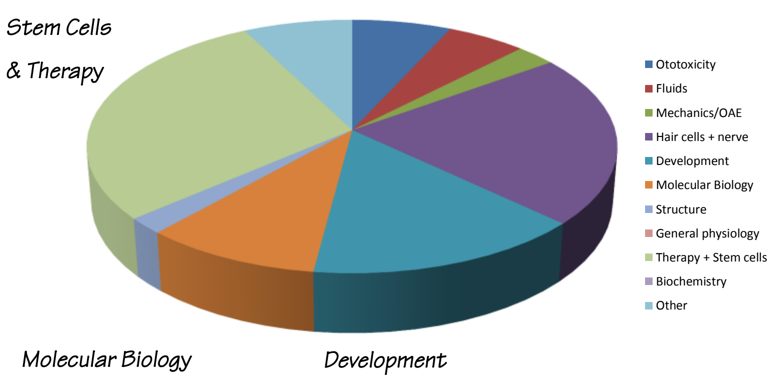




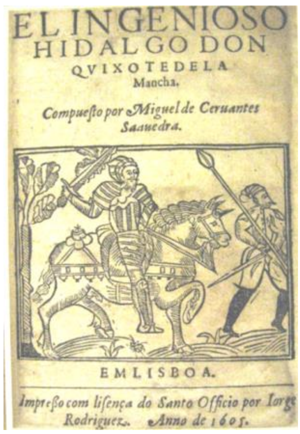




By 2012, the 49th Inner Ear Biology Workshop Tuebingen covered a wide range of topics:



So here we are at Alcala, home of Miguel de Cervantes. Could Don Quixote have been thinking about hair cells? Since the first Inner Ear workshop, the cells have grown larger and occupied a more prominent position in our thinking. We are still tilting at them but, still, they are just as mysterious as ever….


EL INGENIOSO
HIDALGO DON
QVIXOTE DE LA
Mancha.
Compuesto por Miguel de Ceruantes
Saauedra.
EM LISBOA.
Impresso com licença do Santo Officio por Iorge
Rodriguez. Anno de 1605.

What giants?" asked Sancho Panza.

"Those you see over there," replied Don Quixote, "with their long arms. Some of them have limbs well nigh two leagues in length."