Infrastructure and resources in the modern IEM laboratory

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Diagnosis of IEM

- Identification and/or quantification of metabolites in biological fluids (blood, urine, CSF, …) according to clinical phenotype: diagnostic orientation
- Measurement of enzyme activity, incorporation studies: confirmation of diagnosis
- Gene mutation analysis: more and more widely used, sometimes replacing enzyme determination (enzyme defect only expressed in liver, substrate difficult to obtain, …)

Organisation of IEM laboratories

- There is a great diversity in implantation of IEM laboratories
- Often because of historical reasons rather than rational organization
- In the past, biochemical diagnosis of IEM was performed in “general” biochemistry labs
- The growing sophistication of the investigation methods, and the complexity of the diseases, together with the increase of the workload, necessitated the individualization of specialized labs

Organisation of IEM laboratories

- Hospitals with intensive care units need to have clinical chemistry departments able to perform a limited range of tests, such as ammonemia or blood lactate, on a 24h/day emergency basis
- A rapid turn around service for plasma amino acids and urinary organic acids analysis also seems advantageous
- But, results from ERNDIM qualitative schemes have shown that labs with a low workload may perform poorly

Organisation of IEM laboratories

- Moreover, in small structures, interpretation of results often relies only on one specialized biochemist and this is a fragile set up
- Therefore, IEM labs need to be of a certain size with sufficient sample throughput to justify
  - the capital investment required
  - the technical efforts to ensure reliability of the assays
  - the thorough training of specialized biochemists

Minimum equipment of IEM labs

For the identification and/or the quantification of metabolites, each centre requires

- Small equipment for TLC, electrophoresis, …
- Amino acid analyzer
- GC/MS for organic acids and metabolites quantification
- ESI-LC-MS/MS for acylcarnitines and other metabolites (possibly amino acids)
- Mixed usage (for example with a toxicology service) is a non satisfactory solution

IEM labs in academic medical centres

- Cell culture facilities
- Enzymatic assays: spectrophotometer, spectrofluorimeter, radioisotopes,…
- Molecular biology: automated sequencing analyser, …
- Newborn screening

Training of the staff

The actors

- Biochemists
- Technicians
- Engineers
- Quality control and assurance manager

Training of the staff : biochemists

- Specialized in one or few areas of metabolism
- From metabolites, to enzymatic and molecular investigation
- Must work in pairs (vacations, illness, …) or remote access to data
- Essential advisory role to the clinician
- Orientates the investigations to be performed in coordination with the clinician for a rapid and efficient diagnosis at a lower cost

Training of the staff : technicians

- Trained for a group of techniques, i.e. metabolites, enzymology or molecular biology
- At least, work in pairs even for the most sophisticated assays
- Flexible rotation (without dilution of experience !) feasible
- Involved in quality control

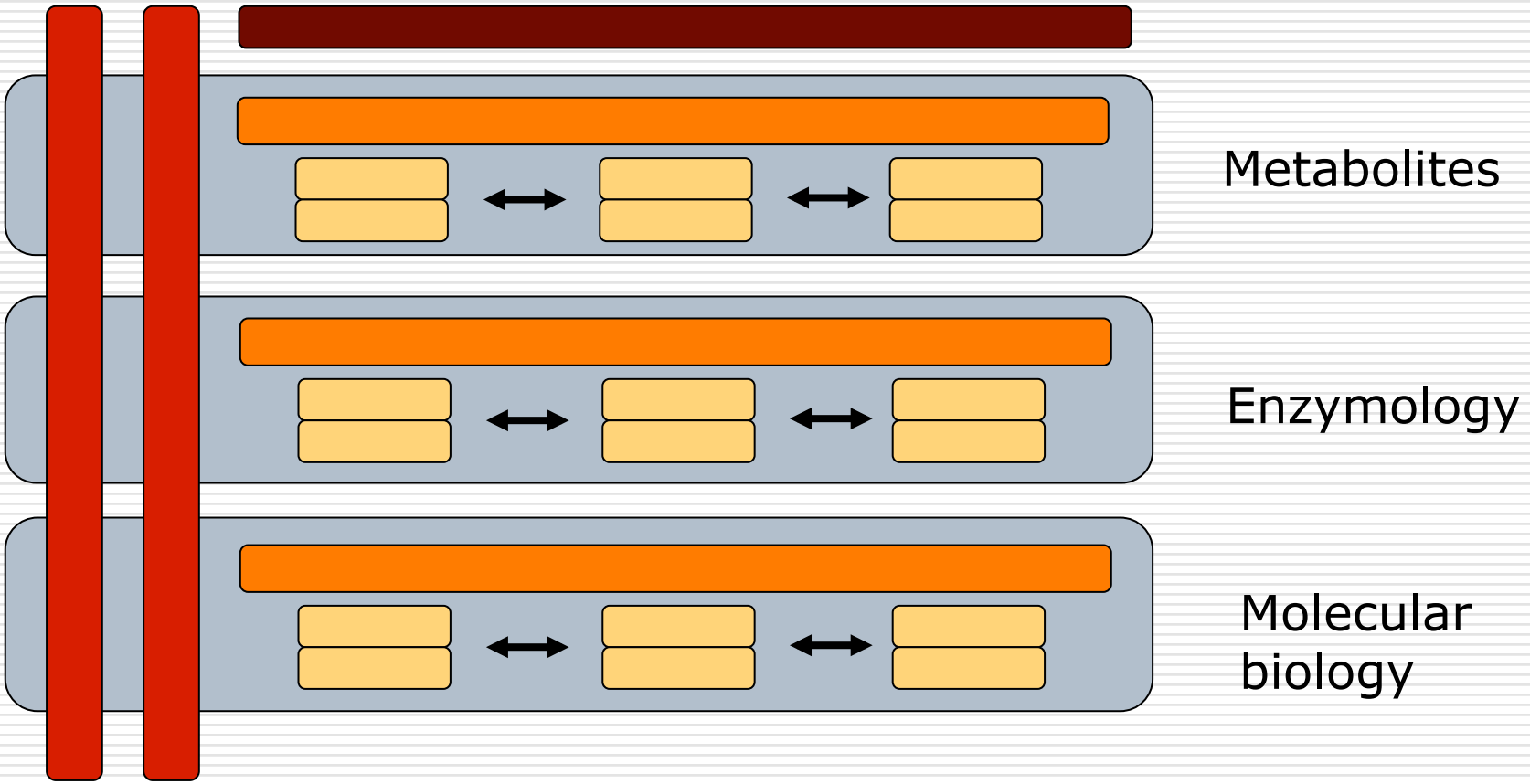
Training of the staff : engineers

- Academic training is “country specific”
- Advantageous in a modern IEM lab
- Involved in the management of platforms: mass spectrometry, molecular biology, …
- Involved in the development, the optimization and the transfer to “routine” of assays
- Intermediary between the biochemists and the technicians

Training of the staff : QA manager

- Technician, engineer or biochemist
- Should be uniquely devoted to quality assurance and quality control
- But few labs have the necessary resources :
  ? sharing within or between institutions

Organization of the “ideal” IEM lab



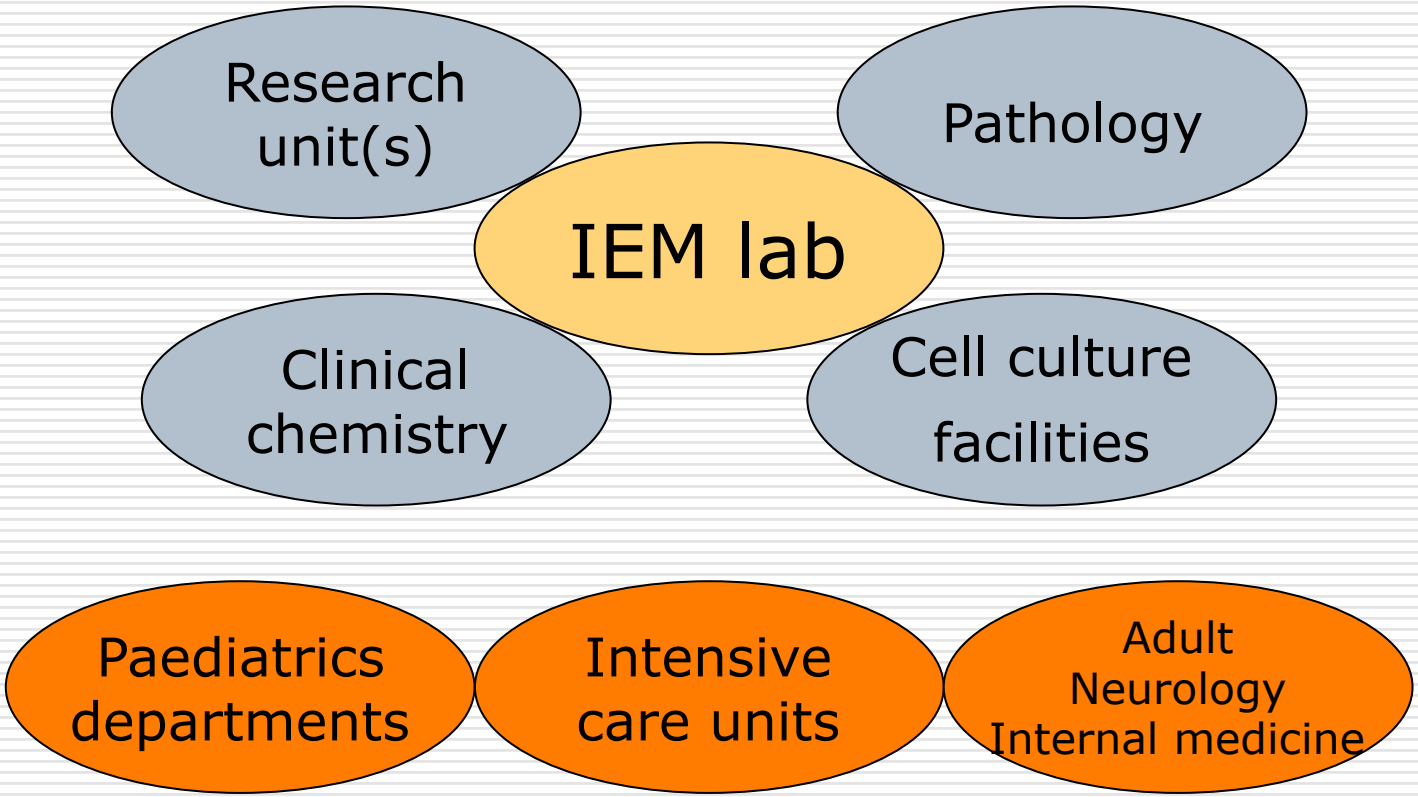
Timetable of the IEM lab

- Monday to Friday : « normal » service
  - Technicians : 8 am to 5 pm
  - Biochemists : as long as needed !
- Saturday : emergency or normal service
  - Three technicians : 8 am to 3 pm
    - Metabolites : new patients, acute decompensations
    - Enzymology : galactosemia, leukocyte preparation, prenatal diagnosis
    - Molecular biology : prenatal diagnosis
  - One biochemist : 9 am to 4 pm
- Or special agreement for variable working time

Interface with research

- Necessary in academic medical centres
- Different possibilities
  - Biochemists share their time between the IEM lab and a research unit
  - The IEM lab hosts a research unit
  - The IEM lab works in close collaboration with a research unit
- Stimulates the development or the evaluation of new biochemical markers

Ideal environment of the IEM lab



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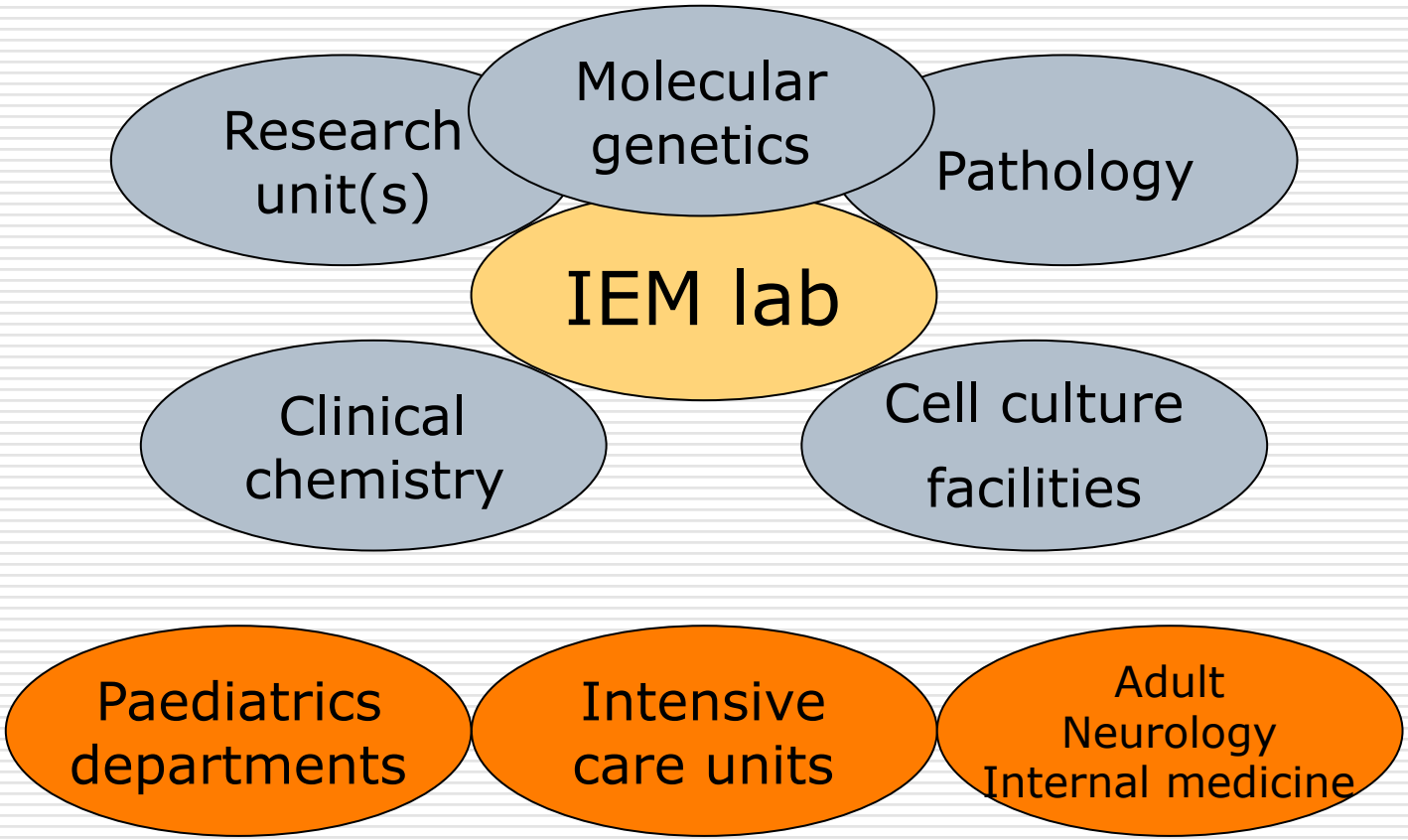

Organization of a network

- No lab can offer the full range of investigations for IEM
- A collaborative networking approach is required
  - Within one country
  - Or international for rare disorders or small countries
- Dialogue and consequent action within one country is necessary to avoid redundant assays and missing investigation: role of national associations and/or professional bodies of biochemists (for example, in France, ANPGM has rationalized the services in molecular genetics)

The challenge of accreditation

- The International Organization for Standardization (ISO) has developed an international guideline for testing laboratories in general (ISO 17025), and one in particular for medical laboratories (ISO 15189). Some countries preferred "local" guidelines such as CCKL in The Netherlands and CPA in the UK
  - ISO 17025 "General requirements for the competence of testing and calibration laboratories"
  - ISO 15189 "Medical laboratories: Particular requirements for quality and competence"
  - CCKL "Praktijkrichtlijn voor een kwaliteitssysteem voor laboratoria in de gezondheidszorg"
  - CPA "Standards for the medical laboratory"

The challenge of accreditation

- Positive side of accreditation : implementing a quality management system, and assuring good quality in testing laboratories, for the benefit of patients
- But fear of changing approaches or of convincing and motivating colleagues to change
- Heavy work load, with no supplementary staff in most labs
- Will be mandatory in many countries within few years (2016 in France)

Conclusion

- Group tests such as organic acids, amino acids and acylcarnitines, or oligosaccharides, mucopolysaccharides and sialic acid TLC, are best performed and best interpreted together in the same lab, by specifically trained biochemists
- Diagnostic efficiency is also directly correlated to the close relationships between clinicians and biochemists. On one hand, we are unable to interpret correctly results without the clinical history, on the other, the clinician is unable to give a precise diagnosis without our help