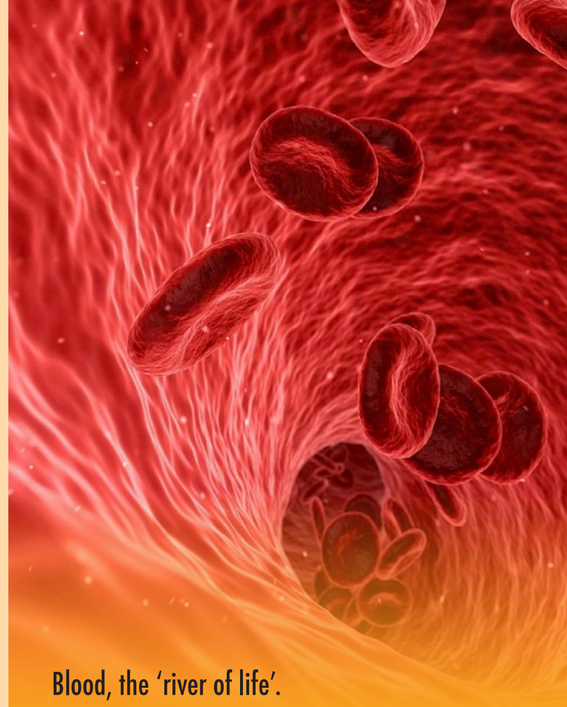
Blood tests: from curiosity to frontline diagnostic aid



Blood, the 'river of life'.

Blood, the 'river of life', circulates to all parts of the human body, perfusing tissues and organs, reflecting their status in health and disease. Methods for measurement of up to 200 blood chemistry analytes have evolved over last two centuries to assist in diagnosis and treatment.

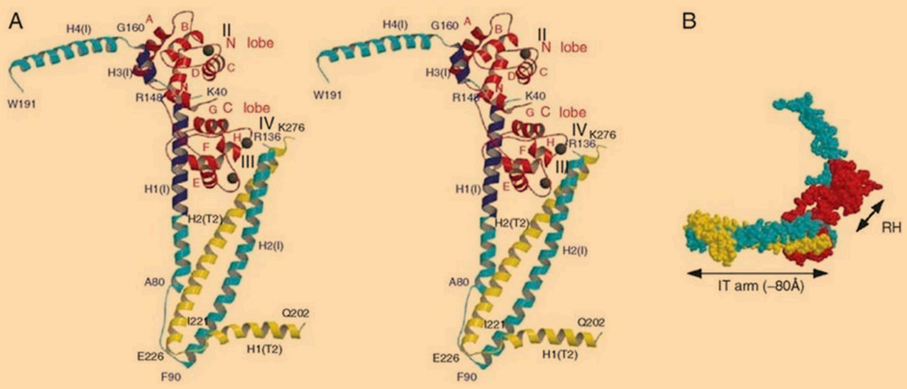
Curiosity and the first blood tests: a background

Blood was regarded as preserver of life and vitality, and most important body fluid in ancient humoral doctrine.

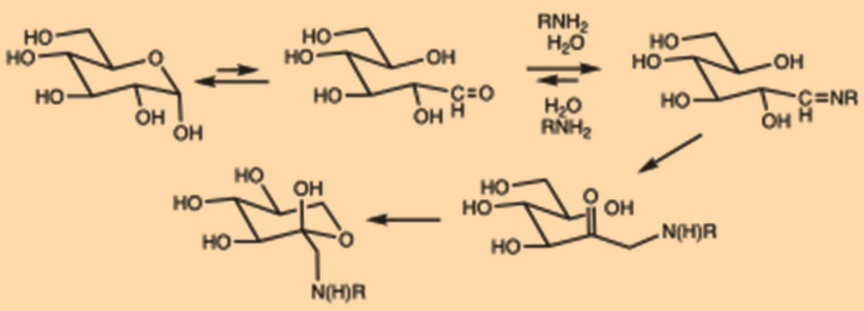
- 1827: At Guy's Hospital in London, physician/chemist John Bostock noted a rise in blood urea in nephritis, possibly the first chemistry blood test.
- 1831: Fired by scientific curiosity with new methods of analysis, William Prout and Alexander Marcet explored the chemical composition of plasma, with significant changes in blood chemistry reported in a number of disease states.
- 1838: George Rees measured blood sugar in diabetes and developed tests for urea and albumin.
- 1848: Alfred Garrod, a physician at University College London, devised an elegant gravimetric test for uric acid and showed an increase in gout.

Systematic approach to developing blood tests: from 1900

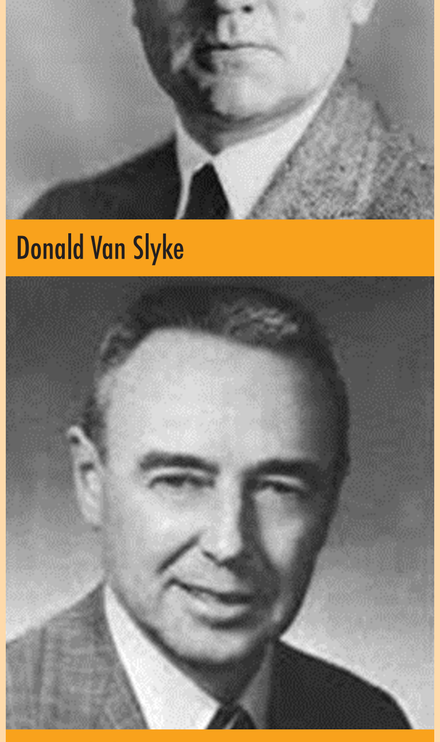
- 1900–1920: Leading US chemists Otto Folin, Stanley Benedict and others devised colorimetric micromethods on protein-free filtrates from whole blood. Tests targeted on significance in diagnosis and monitoring of renal disease, diabetes and disorders of acid base balance. Older techniques such as titrimetry and gravimetry continued for serum sodium and potassium but were laborious, and special skills were required using volumetric and manometric apparatus designed by Donald Van Slyke. Varley reviewing laboratory developments in Manchester recounts that the UK was slow to follow this progress.
- 1922: Discovery of insulin resulted in an increase in blood sugar monitoring.
- 1920–1948: Intensive and 'competitive' research saw new, improved blood tests developed, including for sodium, potassium, urea, creatinine, calcium, magnesium, amylase and alkaline and acid phosphatase, iron, amino acids, protein-bound iodine, paracetamol and salicylate.
- The photoelectric colorimeter gave more precise colorimetric results (1929) and flame emission photometer (1945) more accurate serum sodium and potassium measurements.
- Practical chemical methods in clinical medicine textbooks published between 1924 and 1937 were informative and a guide for laboratories to adopt new and clinically useful blood tests.
- 1947: The quality of blood tests was first surveyed by external evaluation in the USA.



Crystal structure of the core domain of human cardiac troponin.



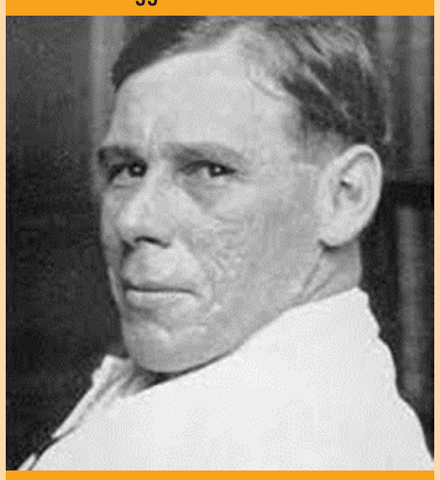
Glycation pathway via Amadori rearrangement (in HbA1c, R is typically N-terminal valine).



Otto Folin

Donald Van Slyke

Leonard Skeggs



Stanley Benedict

Early automation in biochemistry.

Blood testing automated and subject to new technology: from 1948

US biochemist and author Louis Rosenfeld designated 1948 the start of the golden age for blood tests with innovation, new approaches and improved instrumentation. This was to cope with exponential rise in clinical demand for blood tests in post-war decades. This included improved blood collection, with the 'Vacutainer' patented in 1949, and more recently automated blood sample loading, direct sampling and barcodes for sample and test identification.

Automation

Existing analytical procedures were manual and to manage the ever-increasing workload automation was required.

- 1957: Leonard Skeggs at the Technicon Corporation developed the 'Autoanalyser', which was rapidly adopted for commonly requested 'routine' blood tests, notably glucose, urea, creatinine, calcium and uric acid with reduced labour and improved precision. Eventually the sample stream was split to perform six different tests (SMA 6/60), twelve tests (SMA 12/60) and by 1972 included computer control and data handling. Continuous flow systems were challenged by selective discrete or random-access analysers during the following decades.

Van Slyke volumetric apparatus.

Progress Over Two Centuries

The blood test is often the first line of investigation for a patient and remarkable progress has been achieved over the past 200 years. The clinical laboratory can now provide a rapid and reliable analytical service for a huge repertoire of blood tests for accurate diagnostic and therapeutic clinical decisions.

Opportunities for increased clinical and scientific investigation

Immunoassay

Clinical interest in advancing endocrinology and addressing conditions with high mortality and morbidity such as heart disease, cancer and diabetes were driving forces for new blood tests. However, the analysis of very low concentrations of biomarkers, immunoglobulins and hormones would require more sensitive and specific methodology.

- 1959: Nobel Prize-awarded research into metabolism of insulin using radioimmunoassay (RIA) fulfilled the above requirements. Early assays used RIA but in the following decades various platforms such as ELISA and EMIT were introduced, and later use of monoclonal antibodies and non-isotopic labels allowed high-sensitivity automated methods.
- 1980s: Significant blood immunoassays developed including those for thyroid hormones, tumour markers, cardiac troponins, CRP, 1,25dihydroxy vitamin D and HbA1C. Portable analysers have been developed for immunoassays for point-of-care testing including tumour markers, haemoglobin, glucose, troponins and drug screening.

Improved technology

- Atomic absorption spectrophotometry: Progress achieved for serum calcium, copper and zinc, and for blood lead for industrial and environmental monitoring.
- Mass spectrometry: Introduction during the 1990s revolutionised neonatal bloodspot mass screening for inherited conditions and more accurate detection and measurement of drugs.
- Electrophoresis: Various support media included paper, cellulose acetate, agarose and polyacrylamide gel used to improve resolution of plasma proteins or DNA. Capillary electrophoresis found favour in drug screening and molecular diagnostics.
- Chromatography: Different forms – thin-layer, ion exchange and HPLC – have been used for serum amino acids; gas liquid for serum drugs; and affinity for haemoglobin variants and HbA1c.

Blood Lines:
A Resource Not To Be Taken In Vein
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