The History of Contrast Media Development in X-Ray Diagnostic Radiology

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Abstract: The origins and development of contrast media in X-ray imaging are described. Contrast media were used from the earliest days of medical imaging and a large variety of agents of widely different chemical natures and properties have been used. The use of contrast media, which should perhaps be seen as an unavoidable necessity, have contributed significantly to the understanding of anatomy, physiology and pathology.

Keywords: Contrast Media, Pyelography, Angiography, X-ray, Neuroimaging.

I. INTRODUCTION

Contrast media have been used since the earliest days of radiology [1], and developments in medical imaging have not removed the need for their use as might have been predicted. The history of contrast media is complex and interesting and has recently been reviewed by Christoph de Haën [2] . The need for contrast media was well expressed by the pioneer radiologist Alfred Barclay when he said in 1913 that 'The x-rays penetrate all substances to a lesser or greater extent, the resistance that is offered to their passage being approximately in direct proportion to the specific gravity' [3]. Barclay continued by noting that 'The walls of the alimentary tract do not differ from the rest of the abdominal contents in this respect, and consequently they give no distinctive shadow on the fluorescent screen or radiogram.' Barclay clearly states the essential problem confronting radiologists. The density differences that are seen on the plain radiographs are those of soft tissue (which is basically water), bony and calcified structures, fatty tissues, and gas. The liver has the same density as the heart and therefore the two structures cannot be separated on plain films. It was only when the CT scanner was invented by Sir Godfrey Hounsfield [4] that density differences within soft tissues could be readily appreciated, and even with CT scanning the administration of contrast media are commonly needed. We identify structures radiographically when a border is present between tissues of differing radiodensities, and when the tissues are of the same density that border is lost. This is the basis of the *silhouette si*gn that was popularised by Ben Felson from Cincinnati [5]. This sign was first described by H Kennon Dunham, also from Cincinnati, in 1935. Dunham noted that if the left heart border is not visible then this implies disease in the adjacent lung, the lingual segment of the left upper lobe. The basis of contrast media consists in the artificial manipulation of tissue density so that specific structures are revealed, and as Barclay says, 'The method depends on filling the cavities with some substance that differs as widely as possible in density from that of the tissue structures, i.e. by something very heavy such as a bismuth salt, or by inflating them with air or gas.'

II. TYPES OF CONTRAST MEDIA.

Contrast media may be divided therefore into positive contrast media that are of high atomic number, and negative contrast media that are of low atomic number (table 1). Material used for radiographic contrast may be solid, liquid, or gaseous. Liquid contrast media   may be found as solutions or suspensions. The double contrast arthrogram (fig 1) is an example of combining a positive contrast (an iodinated contrast media), which is coating the meniscus, and a negative contrast (carbon dioxide) distending the knee joint.

Fig.1 An example of positive and negative contrast media. A double-contrast knee arthrogram, showing the meniscus outlined with water-soluble iodinated contrast and the joint distended with carbon dioxide gas

Table 1. Positive and Negative Contrast Media.

	Example	Use
Positive	Bismuth subnitrate	Gastrointestinal radiology
	Barium sulphate	Gastrointestinal radiology
	Iodinated contrast media	Many uses including intravascular examinations.
Negative	Room Air	Ventriculography, myelography, cystography.
	Carbon dioxide	
	Oxygen	
Combined positive and negative	Iodinated contrast or barium and gas	Double contrast studies, including barium meals, enemas and arthrograms.

III. THE GASTROINTESTINAL TRACT.

Since, as Alfred Barclay has already indicated, 'The walls of the alimentary tract do not differ from the rest of the abdominal contents in this respect, and consequently they give no distinctive shadow', many considered how it would be possible to show the oesophagus and stomach using Röntgen's new rays following their discovery in 1895. In March 1896 Wolf Becher was able to show the stomach and intestine of the guinea pig using a lead subacetate solution, and in April 1896 Carl Wegele proposed radiography after passing a stomach tube that contained a thin metal wire. In the February of 1897 Lindermann from Hamburg was able to demonstrate radiographically the greater curvature of the stomach using a gastric tube that was covered with fine wire netting. Only limited information could be obtained using an opaque gastric tube. In June and July of 1897 Jean-Charles Roux and Victor Balthazard in Paris were able to observe gastric peristalsis in the frog and dog, and then a human. They used bismuth subnitrate at 200mg/ml of food, and in all three cases divided the stomach into an upper inactive reservoir and an active pre-pyloric region.

The most significant of the early workers was Walter Bradford Cannon, who as a first year medical student at Harvard Medical School, and with his fellow student Albert Moser, started researching the gastrointestinal tract using x-rays. This was following the suggestion of Professor Bowdich. Cannon used bismuth mixed in with bread, meat, mush and viscid fluids. This was fed to a goose and peristalsis was shown clearly with waves of contractions moving regularly down the oesophagus. There was no evidence of squirting from the mouth. This contradicted the current belief that food was pushed into the stomach from the actions of the mouth and pharynx. As a medical student Cannon worked with Francis Williams, who was the pioneer radiologist at Boston City Hospital. In 1898 Cannon assisted Williams in looking at the stomachs of two children [6]. They used a fluorescent screen covered with a sheet of celluloid, which could be marked directly using a pencil with the position of the stomach (fig 2). Radiography was not possible in the very early days because of the low power of the apparatus. Cannon and Williams observed changes in the position of the stomach between the prone position and standing, the movements of the stomach on respiration, and the changes in shape of the stomach during digestion. Whilst

such observations may seem obvious to us today, at that time these basic anatomical and physiological changes had not previously been observed. These observations were innovative and important. Canon made further useful observations on the nature of peristalsis (fig 3) [7].
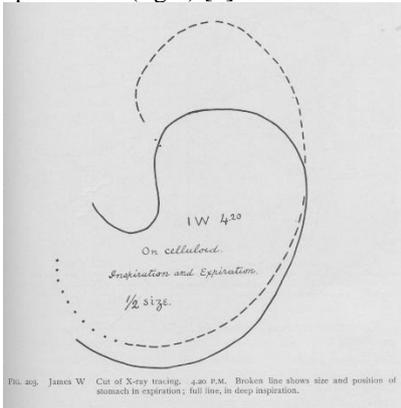

Fig. 2 Cut of X-ray tracing of child examined by Williams and Cannon in September 1899. Stomach outlined by a mixture of milk, bread and bismuth. Broken line shows size and position of stomach on expiration, full line on inspiration, from Williams (1901).
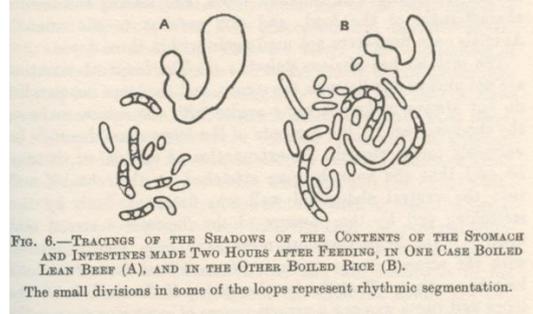

Fig.3 Tracings of the shadows on the stomach and small bowel, from Cannon (1911)

The early radiologists initially used bismuth subnitrate to visualize the human alimentary tract. In the early period drawings were made (fig 4), and as the power of the apparatus improved it became possible to obtain radiographs, even through the dense abdomen (fig 5). Early attempts to use air or gas alone were unsuccessful. The subject was reviewed by Russell Carman and Albert Miller, both from the Mayo Clinic, in 1917 [8] . Bismuth subnitrate was toxic and resulted in some fatalities and so its use was abandoned. It was replaced by bismuth subcarbonate, which was subsequently used extensively. The oxychloride of bismuth was used occasionally, since it was lighter and could be more readily held in suspension. Bismuth salts had been used therapeutically for indigestion since they are alkaline and would neutralise the gastric acid. It was therefore believed that bismuth would also suppress peristalsis and that this would of be of aid in radiography. Other agents used for the opaque meal were oxides of zirconium (marketed as kontrastin) and thorium, and the magnetic oxide of iron.
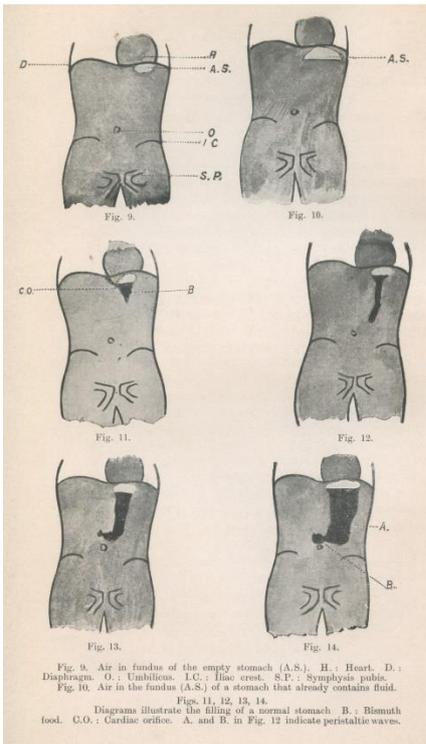

Fig.4 Drawings of the filling of the stomach with opaque meal, from Barclay (1913)

Fig.5 Penetrating gastric ulcer (arrowed) on a single contrast opaque meal, by Sebastian Gilbert Scott in 1913.

Bismuth salts were gradually replaced by barium salts. Barium was found to be equally as satisfactory as bismuth and was less than a tenth of the cost. The barium was manufactured as a finely divided powder, and had to be free of the soluble salts which were toxic. Barium neither inhibited nor suppressed peristalsis, and by the time Carman and Miller were writing in 1917 had largely superseded the use of bismuth.

As the use of barium progressed, there was the need to show fine mucosal detail and so a dense barium reconstituted with water was used. For a double contrast study, pioneered in Japan where there was a high incidence of gastric cancer, an effervescent was swallowed to distend the stomach with carbon dioxide. The double contrast method that was first applied to the colon was promoted in Japan by Shirakabe, Ichikawa and Kumakuru who, by looking at the mucosal pattern on the stomach, were able to diagnose early gastric cancer. The method was both accurate and reliable. The double contrast barium meal was able to demonstrate the stomach and duodenum with remarkable clarity (fig 6). A different barium formulation was commonly used for studies of the small bowel, and an agent was added to prevent flocculation.

The Japanese company Fushimi Pharmaceutical Co. of Kagawa manufactured barium as Barytgen de luxe which was distributed by Eisai Co. of Tokyo. The formulation was successful, and promoted for its high stability against stomach acids, its optimal adhesiveness to stomach mucosa, its constancy in colloidal suspension, and its pleasant taste and odour. They recommended mixing the Barytgen de luxe to water and mixing thoroughly, and preparing the mixture on the night before the day of administration.

The company Schering marketed 'X-opaque' barium as a powder in a 300gm sachet which was to be mixed with 70ml of water. This resulted in a high density suspension, approximately 216% w/v, with a low viscosity. The barium was a blend of precipitated and crushed barium sulphate of varying particle sizes that was said to be essential for good mucosal coating. The barium sulphate was to be powdered into rough particles with jagged edges, and having a size range of 0.5μm to 30μm. For the double contrast technique and effervescent gas-producing agent was used and this needed to be compatible with the barium sulphate preparation. The effervescent granules typically consisted of sodium bicarbonate 44.8%, citric acid 18%, potassium acid tartrate 26.9%, with the addition of a sweetener and flavouring. An anti-foaming and de-foaming agent was needed for both double contrast barium meals and enemas since a bubble might simulate a polyp, and typically 12% w/v of simethicone was added.

For the opaque enema, barium was again mixed with a variety of compounds including condensed milk, fermented milk, or starch. Carman preferred a mixture of mucilage of acacia, condensed milk and barium. Mucilage of Acacia is a viscid liquid used as a soothing agent in inflammatory conditions of the respiratory, digestive and urinary tract. In his classic 1933 textbook book on gastrointestinal radiology [9], the Cambridge radiologist Alfred Barclay recommended adding Tragacanth for both meals and enemas. Tragacanth is a plant and an extract is used to treat both diarrhoea and constipation.

A colonic activator was sometimes added to the barium mixture in the period before the adoption of the double contrast technique. Agents used were oxyphenisatin [10] (marketed as Veripaque) or tannic acid. Veripaque in a dose of 3gm was added to 1 to 2 litres of the barium mixture. The colon was completely filled with the mixture and images were obtained. The barium was voided and the image of the contracted colon gave mucosal detail. Tannic acid and oxyphenisatin stimulated the contracture of the colon, and made the barium sulphate adhere to the bowel wall. The concentration of tannic acid recommended for use in barium enema examinations varies between 0.25 and 3.0 per cent. However neither oxyphenisatin nor tannic acid were without complications [11].

As is the case in a number of areas of human endeavour, just as a technique is perfected it becomes obsolete. Examples include intracranial air studies, oral and intravenous examinations of the biliary tree with iodinated contrast agents, and optimisation of barium for barium examinations. In the 1980s May & Baker marketed EPI-C, for use as a barium enema, as a liquid dispersion for a 1 to 1 dilution with water and for combination with a foam control preparation. The preparation was a barium sulphate suspension 70% w/w (150% w/v) and formulated to provide optimal coating of the mucosa of the large bowel in double contrast barium enemas. The data sheets give little information about what was added to the barium. As with many medications and pharmaceuticals, in the early period they were made locally by pharmacists or doctors and are now produced in factories with minimal local preparation needed, if any at all.
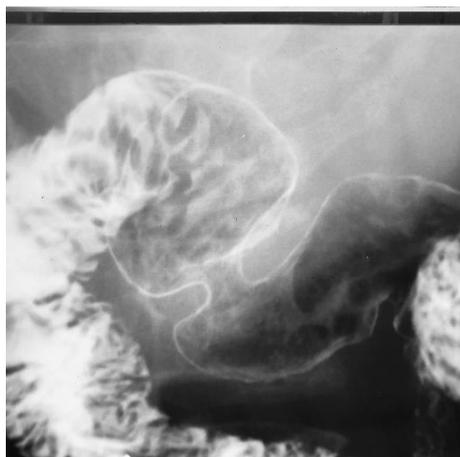
Fig.6 The duodenal cap is demonstrated in this double-contrast barium meal

IV. THE RENAL TRACT.

IV.1. Retrograde Pyelography/Pyelo-ureterography.

That the new rays could be used to investigate the urinary tract was appreciated soon after their discovery in 1895. Before the use of radiography the investigation of urinary disease was not easy. For example, the surgeon could perform a cystoscopy and a ureteric bougie with wax fixed on to its   tip would be passed up the ureter. Any obstruction to the passage of the bougie could be felt and the distance inserted noted, and when removed if the wax was seen to be scratched then this this was evidence a stone. The early apparatus was of low power and visualisation of the abdomen was not easy, although abdominal compression devices were of some assistance. It was only following the development of more powerful X-ray apparatus from about 1905 with 'instantaneous radiography' that the image quality improved. The X-ray shadow pictures, or skiagrams, that were obtained were often confusing and it was difficult to define and differentiate the nature of the calcifications. The calcifications had a number of origins, including calcified lymph nodes, calcified atheroma, ureteric calculi, or to phleboliths. It should be noted that traditionally our radiological techniques were used to confirm a suspected clinical diagnosis, and since the technique was often quite invasive it was only applied when there was a reasonable chance of the examination being positive.

Using the cystoscope it was now possible to introduce a ureteric bougie, which could be followed by abdominal radiography. This was performed by Schmidt and Kolischer independently in 1901, having been suggested by Tuffier in 1898.

Edwin Hurry Fenwick was a urologist at the Royal London Hospital and a pioneer of electrical cystoscopy [12]. Following the discovery of the X-rays Hurry Fenwick recognised the potential of the discovery and became an enthusiastic supported of the new technique. Fenwick had in 1905 developed ureteric bougies with their walls impregnated with a metal for radiographic contrast. Following positing of the bougie at cystoscopy, radiography would be performed and this would demonstrate the course of the ureters and the potential urinary location of calcifications (fig 7). The position of an opacity in relation to the ureter could be determined with confidence, and a phlebolith could be confidently distinguished from a ureteric calculus. Figure 8 was obtained in a 42 year old man with bilateral opaque ureteric bougies. No stone could be felt when the bougie was advanced, and a radiograph was obtained with both bougies in position. A phlebolith is clearly demonstrated outside the ureteric X-ray bougie. Figure 9 shows a comparison radiograph of two ureteric radiographic bougies. The opaque bougie labeled EHF 'stands out in good black shadow', however the bougie labeled 'foreign' 'shows only a faint shadow.' Fenwick notes that it was 'important to secure a radiographic bougie which throws the darkest shadow.' In 1897 he had also used a small fluorescent screen (the cryptoscope) to examine diseased kidneys at the time of operative surgery.   In addition to the radiopaque bougies as a positive contrast, Hurry Fenwick used a negative contrast with air inflation of the bladder (fig 10). The ureteric bougie is in the right ureter and an atheromatous plaque is seen outside the ureter. The central lucency is air in the bladder showing its position.
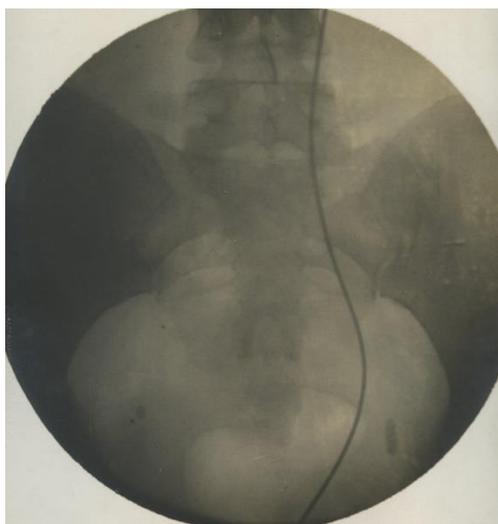
Fig.7 A ureteric bougie impregnated with metal has been inserted in the ureter at cystoscopy. The calcification is outside the ureter. A case of the radiologist Sebastian Gilbert Scott, and the examination probably performed by Hurry Fenwick
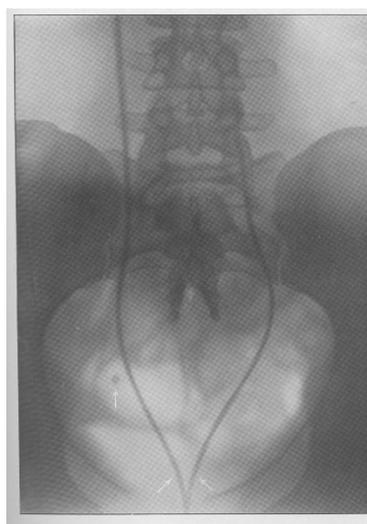

Fig.8 A 42-year-old man with bilateral opaque ureteric bougies (double white arrows). A phlebolith is clearly demonstrated outside the ureteric X-ray bougie on the right (upper right white arrow), from Hurry Fenwick (1908). This would be a time-consuming examination to perform, and would require general anaesthesia.

Hurry Fenwick commented on the distressing situation with the failure of operative surgery when a kidney was opened, and therefore was damaged to some extent, to remove a stone when it was in fact no longer in the kidney and was now within the ureter. Hurry Fenwick estimated that this happened in about 30% of cases when the 'X-ray expert' was not called upon to help in the diagnosis. That the 'X-ray expert' (or radiologist as they came to be called) can 'guide the urinary surgeon (urologist) with a precision unattainable before the introduction of the (X-ray) method is without cavil (or disagreement).' Hurry Fenwick was writing in 1908 when the techniques used were still quite primitive and before the introduction of retrograde or intravenous pyelography. In 1908 Hurry Fenwick produced his well-known book *The Value of Radiography in the Diagnosis and Treatment of Urinary Stone* in which he described his experience with radiography [13]. Hurry Fenwick was one of the first to practice clinical-radiological-pathological correlation, correlating the clinical findings with the radiography and then with the operative findings. Quite remarkably he was teaching operative cystoscopy using a bladder phantom before 1900.
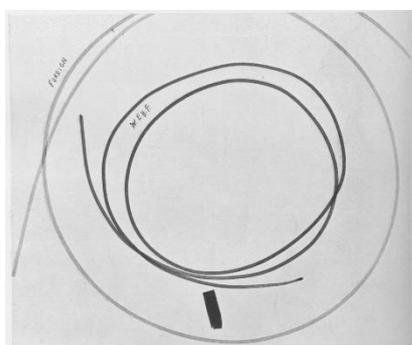

Fig.9 A 'Comparison radiograph of shadowgraph bougies for ureteric examination.' From Hurry Fenwick (1908). The densely opaque bougie labeled EHF is markedly superior to the foreign product.
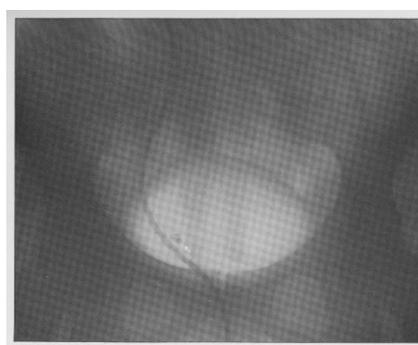

Fig.10 The ureteric bougie is in the right ureter and an atheromatous plaque is seen outside the ureter (white arrow). The central lucency is air in the bladder showing its position. From Hurry Fenwick (1908).

The impregnation of catheters and bougies with material of high atomic number as a contrast material is now used almost universally. The anatomical position of the catheter or medical device may be identified with confidence, and this is essential in angiography, both for diagnosis and to guide intervention. Either the entire catheter may be rendered opaque, or specific parts may be opaque depending on the function of the device. So, for example, the gastric Ryle's tube had metal balls or a marker at its tip for location (Fig 11,) and a tracheal intubating bougie has barium in its tip for improved X-ray guidance. A

further use of contrast material to identify the presence of a device is the use of a radiopaque thread in a surgical swab [14]. If the swab is retained following surgery its presence can be shown by abdominal radiography (fig 12). It is therefore important for the radiologist to know the differing radiographic appearances of medical devices.
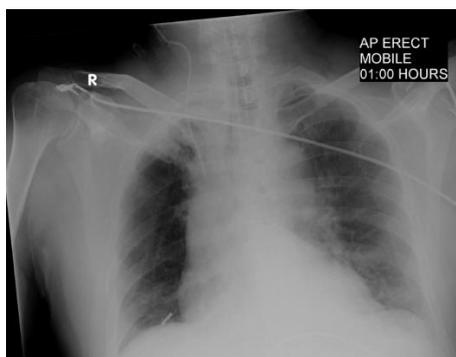

Fig.11 A chest radiograph. The metallic density seen in the lower right lung field is a naso-gastric tube in the right lower lobe bronchus.

Fig.12 A retained surgical swab following abdominal surgery, seen as a coiled dense line on the left side of the abdomen.

Once the use of radiopaque bougies was appreciated, the injection of a liquid radio-opaque material via an opaque catheter was an obvious progression, and was suggested by Klose in 1904. It was already appreciated that the alimentary tract could be outlined with a radio-opaque material such as a bismuth salt, and so a similar technique in the renal tract was a logical progression. For retrograde pyelography or pyelo-ureterography, that is demonstration of the pelvis of the kidney and ureter from below, a suspension of bismuth sub nitrate was initially used, however this procedure was difficult and it was not easy to remove the bismuth from the renal tract. The technique of retrograde pyelography was refined by Voelcker and von Lichtenberg in 1906 and they produced the first complete outline of the ureter and renal pelvis [15]. They were trying to outline the bladder with colloidal silver and on a radiograph noted that the solution had entered the ureter and renal pelvis. They were encouraged by this and therefore injected a 2% solution of Collargol (colloidal silver) followed by a 5% solution of the same (fig 13). The technique was again not without its problems. These were related to the difficulties in inserting ureteric catheters, and in the toxicity of the contrast agents used. The early history of pyelography was well recorded by William Braasch from the Mayo Clinic in 1915 [16] and 1927 [17]. However the technique gradually gained acceptance. Other workers used Argyrol, which was a 40 or 50% solution of silver nitrate. These silver based compounds were toxic to the kidneys and if excessive pressure was used for injection, they sometimes resulted in renal necrosis and some fatalities occurred. In the USA Braasch investigated these compounds extensively, and showed areas of renal necrosis. These severe toxic effects demonstrated the need for safer contrast agents.

Because of the problems with the silver compounds, in 1907 Burkhardt and Polano injected oxygen into the renal pelvis, but the radiographic shadow produced was difficult to distinguish from bowel gas. It was also difficult to maintain a full distension of the pelvis and ureter during the exposure.

By 1915 thorium salts were being used with good radiographic opacification, but a major advance took place in March 1918 when Douglas Cameron, a surgeon from Minnesota, recommended the use of sodium or potassium iodide for retrograde pyelography as a 25% solution [18]. Cameron was aware that halogen salts were of a sufficient molecular weight to give good opacification on radiographs. After some investigations Cameron recommended sodium iodide as the medium of choice, and erroneously thought it was non-toxic even when introduced into the circulation. The 25% solution that he recommended was hypertonic to blood plasma, and as he thought that this might be undesirable, he used a 13.5% solution. His published paper was a preliminary report before he served in the US Navy in the Great War. Experiments showed the better utility of the iodide salt over the bromide as a pyelographic agent. A 14.56% sodium iodide solution was isotonic to a 10% sodium bromide solution and the higher molecular weight of iodide produced a greater radio opacification. Braasch therefore recommended a 12% sodium iodide solution in his book of 1927. Braasch emphasised the importance of the sterility of the solution, which could be boiled and kept in individual containers for each patient. For making larger amounts of the solution sterilization could be performed in bulk by the addition of 1 gram of mercuric iodide for each 3 litres of the 12% sodium iodide solution.

Following the successful introduction of retrograde pyelography, Alexander von Lichtenberg, who was Professor of Urology at St. Hedwick's Hospital in Berlin, undertook extensive laboratory work in an attempt to develop clinical intravenous urography (IVP), but without success. The nearest approach to a successful IVP was achieved by Hryntschalk of Vienna in 1929 [19] who succeeded in producing good radiographic visualisation of the renal calyces and pelves in

laboratory animals after intravenous injection of iodinated pyridine compounds, probably synthesised by Binz and Räth, but he did not disclose the nature of the products, and his work was not fully accepted by the medical establishment.

IV.2. Intravenous Pyelography.

Achieving reliable, safe, diagnostic imaging of the urinary tract was a major objective. Retrograde pyelo-ureterography was an invasive procedure and a procedure that could be performed as an out-patient was essential. In 1923 a multidisciplinary team at the Mayo Clinic described the use of intravenous and oral sodium iodide to visualise the urinary tract [20]. The group comprised ED Osborne who was a syphilologist, CG Sutherland a radiologist, AJ Scholl Jr a urologist, and LG Rowntree the Professor of Medicine. Osborne had noticed that the urinary bladder was visible on radiographs of patients taking large doses of oral and intravenous sodium iodide for treatment of syphilis. The visualisation of the renal pelvis was poor but the authors were able to calibrate the dose of iodine against the urinary iodine concentration and the degree of bladder radiopacity. Sodium iodide was, however, far too toxic for use in clinical diagnosis. Other workers used sodium iodo-urea but these compounds could not be given in large enough doses to produce adequate visualisation.

Arthur Binz and Curt Räth were Professors of Chemistry from the Agricultural College in Berlin. In 1925 and 1926 they synthesised many organic iodine and arsenical preparations that were based on the pyridine ring in an attempt to produce an improved drug for the treatment of syphilis and other infections. The pyridine ring is a six pointed ring made up of five carbon atoms and one nitrogen atom. Linkage to this ring greatly detoxified the arsenic and iodine atoms, and Binz and Räth synthesised more than 700 of these compounds. One group of iodinated pyridine compounds was found to be selectively excreted by the liver and kidney and was therefore called the Selectans. Some of these synthesised pyridine drugs were therefore sent to several clinicians for evaluation for the treatment of biliary and renal infections.

In 1928 Moses Swick, who was working as a urology intern at Mount Sinai Hospital in New York, was awarded the Libman Scholarship to perform medical research overseas [21]. He chose to work with Professor Leopold Lichtwitz at the Altona Krankenhaus in Hamburg, Germany, where he had some success in the treatment of human biliary coccal infections with some of Binz and Räth's iodinated Selectan drugs. Since these drugs contained iodine, it occurred to Swick that they might be of value in visualising the renal tract by X-rays. Swick then made radiological, chemical and toxicological studies in laboratory animals and patients. The initial studies were encouraging and Swick transferred his work to gain access to the large number of patients at the urological department of Professor Alexander von Lichtenberg at St Hedwig's Hospital in Berlin. The first successful human intravenous urograms were produced with the non-ionic N methyl-5-iodo-2 pyridone (Selectan neutral) but Swick preferred the less toxic, more soluble salt 5 iodo-2-pyridone-N-acetate sodium (Uroselectan) that had been patented by Räth in May 1927. This new compound Uroselectan produced excellent quality intravenous urograms with relatively little toxicity (fig 14).
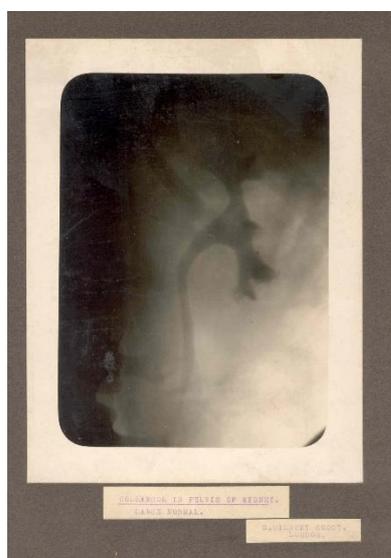

Fig.13 A retrograde pyelogram, with Collargol in the renal pelvis. A case of the radiologist Sebastian Gilbert Scott, and the examination probably performed by Hurry Fenwick
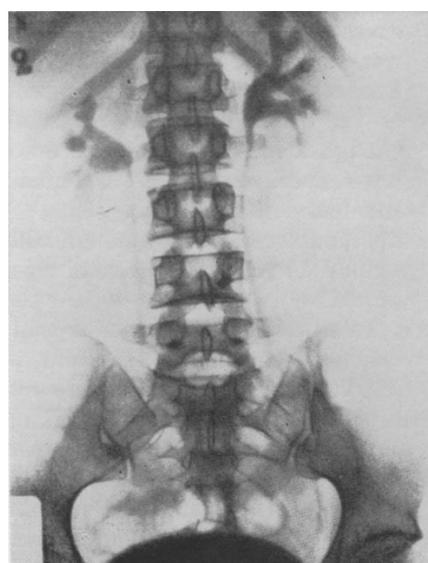
Fig.14 Early IVP from Swick (1929). A 22-year-old female with recurrent pyelonephritis. Note the high quality of the study and the dense pyelograms

Swick and von Lichtenberg presented the work to the Ninth Congress of the German Urological Society in September 1929. Swick presented the first paper based on the animal work but with several excellent quality human studies exhibiting

various disease processes (e.g. hydronephrosis and horseshoe kidney).   Von Lichtenberg and Swick together presented the second paper on the human clinical uses with the paper read by von Lichtenberg. The two papers were   published   in November 1929 in Klinische Wochenschrift [22, 23].

Unfortunately Swick and von Lichtenberg could not agree on who should be accorded priority of discovery of this new and revolutionary technique [24]. Assigning priority in any discovery is always difficult. The reality is that   Arthur Binz and Curt Räth synthesisied the agents used, Moses Swick performed essential clinical and laboratory research, and Alexander von Lichtenberg had a long-term goal of the IVP and provided the facilities and resources. The IVP or intravenous urogram (IVU) as it became known was the result of the work of many different groups over many years.

V. Contrast media design.

V.1. Early Contrast Media.

Within two years following the introduction in 1929 of Uroselectan into clinical practice, Binz and Räth made two further modifications to the pyridine ring. These were marketed as diodrast (Diodone) and neo-ipax (Uroselectan B, Iodoxyl). Each molecule   contained two iodine atoms. Binz and Räth were fully supported by the Berlin based company Schering Kahlbaum in the development of these pyridine agents, and as a result Schering became the world's leading manufacturer of intravascular contrast agents. These compounds, and their variants, were highly successful, and became the standard intravascular and urologic contrast media for the next 20 years.

Moses Swick continued his interest in contrast media. He was working at Mount Sinai Hospital in New York   with Vernon Wallingford (b.1897) who was a research chemist from Mallinckrodt Chemical Works of St. Louis. In 1933 they introduced the six-carbon atom benzene ring as the iodine carrier instead of the five-carbon atom and one nitrogen atom heterocyclic pyridine ring that was used by Binz and Räth.   A difficulty that was encountered using Swick and Wallingford's original benzene ring compound (sodium iodohippurate) was its toxicity, so it cannot be seen as a major clinical improvement. The use of the benzene ring was an important innovation and in 1933 they were awarded the Billing's Gold Medal of the American Medical Association.

There a number of changes that had to be made to the benzene ring before its iodinated derivatives were suitable for clinical use. These were:

1. Approximately twenty years later, Wallingford showed that if an amine group were to be introduced into the meta position (C3), then it allowed three iodine atoms to be introduced at C2, C4 and C6. An amine in the ortho (C2) or para (C4) position allowed only two iodine atoms to be introduced.
2. In 1953 Wallingford   demonstrated that an amine (-NH2) group at the C3 position allowed a side chain such as acetyl (-COCH3) to replace one of its hydrogen atoms [25]. This acetyl-amino group significantly   reduced the toxicity of the tri-iodo compound and sodium acetrizoate (marketed as Urokon and Diaginol) was introduced clinically in 1952 by Mallinckrodt. This was the first tri-iodinated contrast medium.
3. In 1956 Hoppe and colleagues with others demonstrated that a second acetyl amino- group could be added to the benzene ring at the C5 position to produce a fully substituted tri-iodinated acid radical [26]. The toxicity was reduced even further. This compound sodium diatrizoate was introduced in the mid-1950s as Urografin (Schering AG, Germany), Renografin (Squibb, USA) and Hypaque (Sterling Drug). Sodium diatrizoate and its derivatives became the standard intravascular contrast agents until the development of the lower osmolar and non-ionic agents in the early 1970s. Urografin remains in use today as a 30% solution for cystography and retrograde urography (pyelography).

In 1959 the small Norwegian pharmaceutical company Nyegaard & Co. of Oslo were accused by Schering of infringing their patent on diatrizoate, which they thought had not been patented in Norway. Following this, Nyegaard tried to synthesise diatrizoate by another means, and developed a new fully substituted tri-iodinated benzene ring compound (metrizoic acid), which they then marketed as Isopaque (Triosil).

V.2. The Cation.

The   conventional tri-iodinated contrast agents (diatrizoate, iothalamate, metrizoate) designed for intravascular use are ionic monomeric salts of tri-iodinated fully substituted benzoic acids and are referred to as high osmolar contrast media (HOCM) because of their very high osmolality.   The only chemical difference between them is in the nature of the substituted side chains.

In the 1960s it became apparent that the cation used was important. Each of these newer intravascular contrast media molecules were a salt, comprising   three radio-opaque atoms of iodine and one cation. The cation was either sodium or N-methylglucamine (meglumine), or a mixture of the two, as the non-radio-opaque cation necessary to produce the salt molecule. Meglumine produced less pain and less vasodilatation when injected into arteries, but it produced more diuresis and was therefore not ideal for urography. Vosse in 1960 showed that the sodium salt produced more damaging effects on the blood brain barrier and in 1964 Gensini and di Giorgi demonstrated an increased myocardial toxicity when pure sodium salt solution was used for coronary arteriography [27].

For coronary angiography a mixture of sodium and meglumine salts is essential to minimise cardiac arrhythmia. Sodium cations produced less viscous solutions than meglumine and therefore a mixture of the two was often preferred. The balance of cations was further investigated by Nyegaard and in 1963 and 1965 they introduced several versions of Isopaque with a balance of sodium, meglumine, magnesium and calcium salts, different formulations being recommended for cerebral, coronary, vascular and urinary tract visualisation.   Contrast media were marketed in various formulations and concentrations depending on the precise clinical need.

V.3. Low Osmolar Contrast Media.

Torsten Almén is a Swedish radiologist interested in contrast media, who was working at Malmö (fig 15). He studied the pharmacology of contrast agents and believed that the very high osmolality of the high-osmolality contrast media, that is up to eight times physiological osmolality, was responsible for much of its toxicity. He was doing angiography on a daily basis and could observe how painful the patients found the injections. Almén knew that an arterial injection of contrast medium that was isotonic to serum, such as a suspension of thorium dioxide or and emulsion of iodised oil, did not produce pain. Almén grew up on the most southern coast of Sweden and recalls a family holiday taken as a boy in Bohuslän on the west coast of Sweden. He found swimming in the water uncomfortable because as soon as he opened his eyes they started to hurt. The salty water at Bohuslän made his eyes sore whereas the brackish water around Ystad did not cause any discomfort. He reasoned that 'a plasma-isotonic aqueous solution of contrast medium molecules might not cause pain, and should therefore be created!' Almén reasoned that an isotonic contrast medium would both cause less pain and also be less toxic.

Almén taught himself the relevant chemistry and suggested reducing the osmolality of contrast media by substituting the non-radio-opaque cation by a non-ionizing radical such as an amide. His paper on this topic was prepared when he was a Research Fellow in Philadelphia in 1968 to 1969. His thesis, which was completely theoretical and unsupported by chemical or clinical research, was rejected by the leading radiological journals but was eventually accepted and published by the *Journal of Theoretical Biology* in 1969, a journal of which most radiologists were unaware [28]. As a result, the most important paper on contrast media since Moses Swick's 1929 paper was lost to the radiological publications.

Almén's ideas were rejected by several pharmaceutical manufacturers but Hugo Holtermann, the Research Director of Nyegaard, encouraged his team to attempt synthesis of some of Almén's theoretical molecules. The research team at was not fully convinced that Almén's proposal could be implemented, and Holtermann who was the developer of Isopaque was unsure as to their likely success, however they were willing to try Almén's ideas. Almén also made known his ideas as to how these compounds might be constructed to facilitate water solubility and hydrophilicity and to reduce their viscosity. It is remarkable that fewer than 6 months were to elapse between the first meeting of Almén and the Nyegaard research group in June 1968 and the production of the first compound [29]. The team produced 80 different compounds. A consultant reviewer of Almén's 1969 paper stated 'The general principles of Dr. Almén's proposal are probably sound. The implementation of it is probably impractical. He seems to be unaware that the ionic nature of the iodinated compounds is an essential property for their solubility in water—so part of his proposal, namely using non-ionic hydrophilic compounds, may be invalid'.   In November 1969 after biological and pharmacological testing, compound 16 (called 'Sweet Sixteen') was shown to be the most promising and it was marketed as Amipaque, the first low-osmolar contrast medium (LOCM)). Amipaque was based on the glucose amide of Isopaque (metrizoate) leading to its generic name of metrizamide (Amipaque). As it contained the glucose radical, metrizamide could not be autoclaved. Because of the complex nature of its production, it was expensive and inconvenient to use, being presented as a freeze-dried powder with a diluent. It was, however, a major toxicological improvement on all pre-existing water-soluble myelographic and vascular agents and in the late 1970s it became the internationally recognized agent for myelography, enabling water-soluble myelography to replace oily Myodil (Pantopaque) myelography. Although it had an advantageous intravascular profile, metrizamide was generally regarded as

too expensive and too inconvenient for vascular studies. In recognition of his achievement Torsten Almén was presented with the Antoine Béclère Prize at the 1989 World Congress of Radiology.

In the mid-1970s, metrizamide was supplanted by the second generation of low osmolar contrast media. These were Iohexol (marketed as Omnipaque by Nycomed previously called Nyegaard) and Iopamidol (marketed as Niopam by Bracco of Milan) which were easier to synthesise and were therefore much less expensive. They did not contain the glucose radical and could therefore be autoclaved and were stable in solution. These two second generation LOCM, together with similar molecules, became the contrast media of choice for all intravascular procedures in the mid 1990s [30]. Omnipaque was almost completely excreted by the kidneys and was of very low toxicity.

V.4. Myelographic Agents.

Prior to 1970, only iodinated oils such as iophendylate (Myodil, Pantopaque) were available for myelography. Ionic compounds such as meglumine iothalamate (Conray) and methiodal (Abrodil) were generally considered too irritant and toxic, although they were occasionally used for lumbo-sacral radiculography.

The French company Guerbet, following original research performed by Mallinckrodt, developed the ionic compound meglumine iocarmate (Dimer-X) combining two tri-iodinated benzene rings into one large dimeric molecule containing six atoms of iodine and so reducing the osmolality. Dimer-X could only be used in the lower portions of the spinal canal below the spinal cord for radiculography but it produced excellent quality radiographs of the lumbo-sacral nerve roots. It was presented as a 60% w/v solution, and unfortunately its high osmolarity was responsible for some of the adverse reactions. It was promoted for use in lumbo-sacral radiculography, cerebral ventriculography, and double-contrast knee arthrography. Though much less toxic than the previous aqueous contrast media, it had to be used with great care and in a strictly limited dose. By contrast, metrizamide could be used throughout the spinal canal and was much less toxic than meglumine iocarmate, which it replaced for myelography and radiculography in the late 1970s.

V.5.i. The Second Generation Low Osmolar contrast Media.

The introduction of metrizamide revolutionised the use of contrast agents and marked the boundary between the older conventional ionic high osmolar media (HOCM) and the modern low osmolar compounds (LOCM). Iohexol and iopamidol were the first two second generation non-ionic LOCM agents to be synthesised and in the 1990s were the intravascular and myelographic agents of choice.

In 1977 the French company Laboratoire Guerbet produced a new contrast agent of low osmolality, which was a derivative of meglumine iocarmate (Dimer X). This new molecule consisted of two tri-iodinated benzene rings that were linked together, and it was therefore a dimer. The dimer had one carboxyl group replaced by a non-ionising radical. The second carboxyl group was attached to either a sodium or meglumine cation. The resulting product (sodium and meglumine ioxaglate [31], marketed as Hexabrix 320) proved a good arteriographic agent but often caused nausea and vomiting on intravenous injection. Being ionic Hexabrix was not suitable for myelography or radiculography.

V.5.ii. Non-ionic dimers.

In order to reduce the osmolality even further, two molecules of non-ionic monomers have been linked to produce a large non-ionising molecule containing six atoms of iodine. Such products include visipaque (Iodixanol) and iotrolan (Isovist), which are of physiological osmolality at all concentrations. These non-ionic dimers were believed to have advantages for myelography and be beneficial for arteriography. These new agents have additional benefits and are significantly less nephrotoxic [32] .

Torsten Almén has reviewed the development of the non-ionic contrast media [33]. Development has resulted in agents isotonic with plasma and causing less pain and toxicity. The current agents in use for X-ray examinations are tri-iodinated, non-ionic contrast agents. It has been the development of these safe contrast agents that has greatly facilitated the development of modern radiology in general, and of interventional radiology in particular.

V.6. The Graham Test and Biliary Contrast Agents.

In the early 1920s the diagnosis of gallbladder disease was largely related to having a typical history and to physical examination. Everts Graham, who was Professor of Surgery at Washington University in St. Louis, knew that the opaque meal could outline the alimentary tract and was looking for an opaque substance that could be introduced into the

gallbladder. In 1909 Abel and Rowntree had noted that 90% of orally administered phenoltetrachlorophthalein was excreted by the liver. Graham and Warren Cole thought that bromide and iodide compounds of phenopthalein could be tried experimentally. The first compound used was tetraiodophenolpthalein, and good results with opacification of the gallbladder were obtained in dogs. The technique was introduced into clinical practice as the Graham test after it was announced in 1924 [34] . In 1933 Barclay described both oral and intravenous administration of the agent.

The agents were slowly perfected, with the introduction in the 1970s of Endobil (the N-methylglucanine salt of iodoxamic acid) for cholecystography and cholangiography, and Biliscopin (meglumine iotroxinate) for intravenous cholangiography. It must have been quite frustrating for the contrast media companies who had devoted time and money in the synthesis and testing of these newer agents, that as they were optimised they became obsolete being replaced by ultrasound and MRI.

VI. ANGIOGRAPHY.

VI.1. Post-Mortem Angiography in Vienna.

It is remarkably how rapidly ideas about visualisation of the soft tissues of the body with contrast media developed. In the case of the alimentary tract it was possible immediately to demonstrate anatomy and physiology *in vivo*. This was not to be the case in the vascular system until non-toxic agents were developed. However that angiography could be performed post mortem using non-physiological and toxic agents demonstrated that vessels could be visualised, and held out the possibility of clinical use when physiological agents were developed.   There is considerable current interest in post-mortem angiography [35] and virtual autopsy or 'virtopsy' [36] , and it should be remembered that angiography developed from post-mortem studies [37]. The first angiographic procedure was performed in January 1896 by the physicist Edward Haschek and his medical friend D Th Lidenthal. They injected a calcium carbonate emulsion (Teichmann's mixture) into an arm that had been separated from a cadaver (fig 16). The exposure time was   57 minutes, which is not unreasonable when one remembers the low power of the apparatus that was then available. This procedure was performed in Vienna, and the radiograph can be seen at the Museum in the Josephinum (Währinger Straße 25. A - 1090 Wien). Sigismund Exner was professor of physics at the University of Vienna and was a friend of Wilhelm Röntgen, and had received a personally dedicated copy of the first communication and a collection of radiographs. The hand used for the experiment was provided by Dr. Julius Tandler who later became the Professor of Anatomy in Vienna.

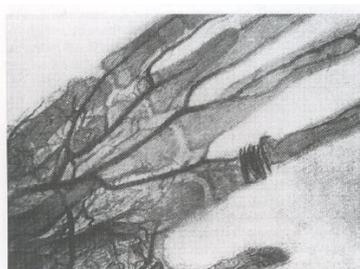Fig.15 Torsten Almén, the designer of metrizamide and LOCM

Fig. 16 The first angiogram of the hand from January 1896, made by Haschek and Lidenthal.

VI.2. The New Photography in Sheffield.

The angiographic work in Vienna was soon followed by the work of the group in Sheffield, England. Prof. Hicks, who was the Principal of Firth College in Sheffield, and Dr. Addison, achieved both a renal and a hand arteriogram [38]. Radiological work had been started at Firth College in Sheffield on February 1, 1896. Hicks and Addison injected specimens that were available in the medical school with red lead and their results were published later that month in the British Medical Journal of 22 February 1896 in an article entitled The New Photography In Sheffield. The apparatus was simple and consisted of an ordinary battery of cells with an induction coil and a Crooke's tube. The apparatus was of low power and the current was never above the strength of one that would give a spark of 3 inches. In their earlier experiments the exposure time varied between 20 minutes to half an hour however they stated that more recently they had obtained good shadows of the bones of the fingers using an exposure of a minute and a half. The Crookes tube was used with a glass shield, with a window in it of about three quarters of an inch in diameter. The vascular injections had been performed by Dr. Addison in

the medical school and on February 6 1896 he had injected samples using the ordinary red lead mass, which was used in the dissecting rooms showing radiographic images of the arteries in the hand and kidney. The hand was nailed to a half-inch wooden board and injected, whereas the kidney was simply laid on to a photographic plate, which had been previously wrapped. The delicate branching pattern of the arteries in the kidney and hand were shown in a similar manner to those that had been demonstrated in Vienna a few weeks earlier and have fascinated the observers.

VI.3. William Morton.

William J Morton MD was an important early figure in radiology in the United States. Morton was 'Professor of Diseases of the Mind and Nervous System and Electro Therapeutics' in the New York Post Graduate Medical School and Hospital. His book *The X-Ray or Photography of the Invisible* is undated, however the preface is dated September 11, 1896 [39]. Morton's co-author was Edwin Hammer who was an electrical engineer. This book was written following the huge worldwide interest that had taken place following the discovery of x-rays by Wilhelm Conrad Röntgen. This book is important because it is the first book on radiology written by a physician. Morton covers all areas of radiology known at the time with speculations about potential future uses for the new rays. Morton makes the very pertinent observation that:

'In teaching the anatomy of the blood vessels the X Ray opens out a new and feasible method. The arteries and veins of dead bodies may be injected with a substance opaque to the X Ray, and thus their distributions may be more accurately followed than by any possible dissection. The feasibility of this method applies equally well to the study of other structures and organs of the dead body. To a certain extent, therefore, X Ray photography may replace both dissection and vivisection. And in the living body the location and size of a hollow organ, as for instance the stomach, may be ascertained by causing the subject to drink a harmless fluid, more or less opaque to the X-Ray, or an effervescent mixture which will cause distension, and then taking the picture.'

This passage is quoted fully because Morton's words are so very perceptive. In this very early book, which was written less than a year following the discovery of X-rays, Morton is not only predicting contrast gastrointestinal studies, but also the use of radiology in the equivalent of modern virtopsy. The pioneers so often realise the exact significance and importance of their observations. Morton had immediately seen that the radiological examination of the body, either living or dead, could produce more information than could be found in either the anatomy theatre or the pathology department.

VI.4. H C Orrin and his Atlas.

The first X-ray atlas of the arteries of the body was written by H C Orrin, and was published in 1920 as *The X-ray Atlas of the Systemic Arteries of the Body* [40]. Orrin is described as a Civil Surgeon who was attached to the 3rd London General Hospital RAMC (T) located in Wandsworth. The book is beautifully illustrated with many high-quality radiographs. The book was designed to be used by students of anatomy, surgical anatomy, and of operative surgery. The book depicts a series of natural illustrations of the systemic arteries in continuity, and precisely as they exist in situ in the undissected body (figs 17, 18). The aims of the book were therefore purely anatomical in nature. Orrin wrote in his introduction that:

'No matter how well dissection is performed, complete continuity of the vessels; their exact relationship to bones; their finest terminal branches; the series of anastomosis into which they enter are seldom if ever accurately displayed or intelligently appreciated by dissection alone.'

Orrin therefore echoes the previous words of William Morton. The beautiful illustration of the coronary arteries prefigures modern coronary arteriography (fig 19). The atlas was accompanied by a full set of stereoscopic radiographs which could be cut out and viewed with a hand-held stereoscope (fig 20), 'which provide the only possible means of accurately rendering visible the points and details specified.' It is fascinating that in 1920 Orrin recognizes the value of 3-D angiography, which is obtained in modern reconstructions of cross-sectional imaging.
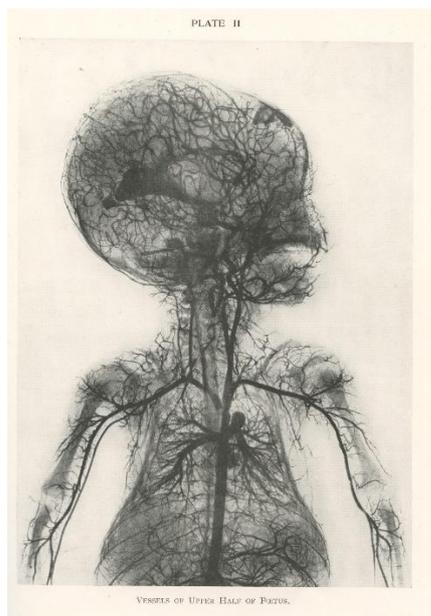
Fig.17 The systemic vessels of the upper half of the body, from Orrin (1920).
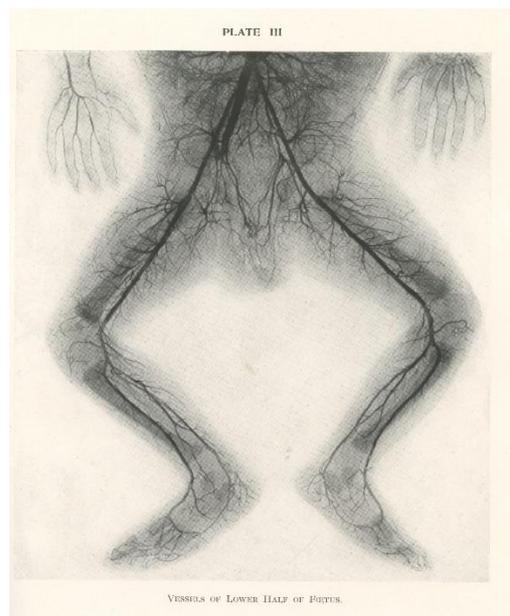

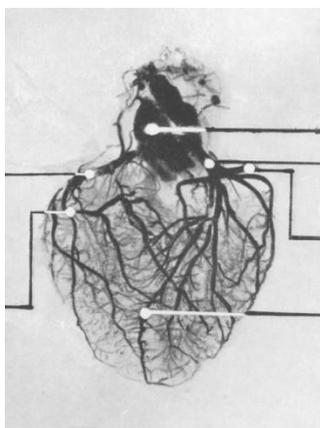Fig.18 The systemic vessels of the lower half of the body, from Orrin (1920).

Fig. 19 The coronary vessels beautifully depicted, from Orrin (1920).
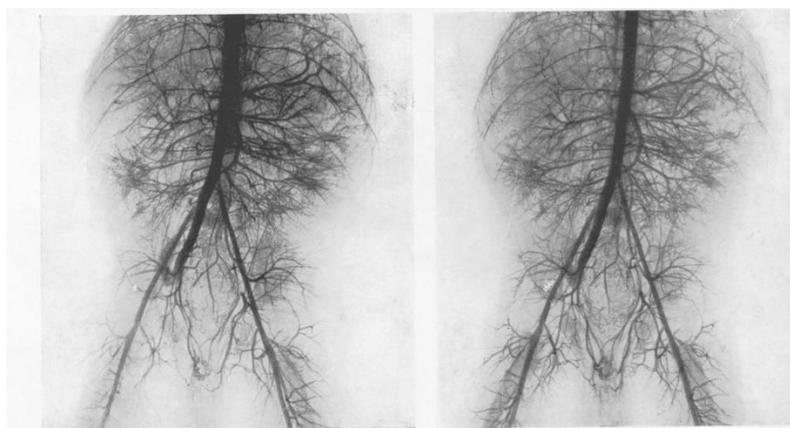

Fig. 20 Stereoscopic radiographs of the abdominal vessels. The plate was designed to be cut out of the book and viewed in a hand-held stereoscope. From Orrin (1920).

VI.5. Egas Moniz and the Portuguese School of Angiography.

From the earliest days of the application of X-rays, in vitro or post mortem angiograms had been obtained [41], and its early history has been reviewed   by Dolby [42]. The main problems encountered related to the nature of what was injected and to its toxicity. Direct puncture and/or cut down arteriography was achieved in the early 1920s by Brooks using sodium iodide and bromide solutions [43] , and by Berberich and Hirsch who injected   Strontium Bromide into the femoral artery of a living subject and obtained useful images [44]. The major breakthrough in angiography was achieved in the Santa Marta Hospital in Lisbon, Portugal on 28 June 1928 when the first successful human carotid arteriogram was performed.

It was thanks to the work of   Portuguese radiologists that the goal of practical angiography in the living was finally realized.   The two key names are those of Egas Moniz, and Reynaldo dos Santos. Veiga-Pires and Grainger have reviewed his outstanding contribution and that of his Portuguese colleagues in the development of arteriography [45].

The charismatic leader of the Portuguese team was Egas Moniz, who was Professor of Neurology in Lisbon. Moniz was a brilliant polymath, author, politician (he was the Portuguese Foreign Secretary), researcher and clinician. Moniz went on to develop the now discredited technique of pre-frontal leucotomy and for this Moniz received the Nobel Prize in 1949. Moniz

was severely handicapped by gout which affected his fingers, and although he was unable to make any injections himself, he meticulously planned his research project on the diagnosis and localisation of cerebral tumours.

Moniz was dissatisfied with the recently developed technique of ventriculography, which he found could make a correct diagnosis in less than a third of patients. At this time there was little known about the use of intravascular injection of radio-opaque substances. Moniz had been aware of the pioneer work of the Frenchmen Jean Sicard and Jacques Forestier in early angiography. They had tried with an intravascular injection of Lipiodol, an oily contrast medium, but their experiments were unsuccessful. Moniz's desire to directly show the brain prefigures modern cross-sectional imaging with intra-venous contrast enhancement. Moniz and his team made experiments on animals and cadavers and showed satisfactory radiographic appearances with arterial injections. Moniz produced a classification of the cerebral arteries in 1928 based on his cadaveric studies, and this was to prove useful in interpreting angiograms in the living subject.

Moniz had reasoned that if he could concentrate radiopaque material within the brain then the brain would become visible on radiographs. Moniz made experiments in 1926-27 with dozens of substances in various concentrations placed in small rubber tubes and radiographed inside a dry skull. The tubes were of a bore similar to that of the larger cerebral arteries. He knew that bromides were used as sedatives, so since they accumulated in the brain they might show up on radiographs. Moniz gave large amounts of bromides orally but showed nothing. He then tried injecting bromine directly into a carotid artery but apart from giving the patient a headache he again showed nothing. Moniz then attempted opacifying the brain itself by intravenous or parenteral administration of a variety of agents, giving large doses of lithium bromide and strontium bromide. The patients chosen suffered either from severe epilepsy or Parkinson's disease, since it was thought that at the very least such patients would benefit from the injected bromine. When 10ml of a 30% solution of strontium bromide was administered the patient had no symptoms. When higher concentrations were used there was a feeling of warmth, and at over 40% the patient developed more generalized symptoms, but they were not prolonged. Moniz finally determined that a 10ml of a 70% solution of strontium bromide produced satisfactory opacification of the cerebral arteries.

Moniz then made intra carotid injections in four patients using a percutaneous injection but showed little. Partly because of patient movement related to pain. He then tried exposing the carotid artery and 4ml of 70% strontium bromide was injected. It was felt that the agent was being diluted, and so an injection was made following a temporary ligation of the carotid artery below the point of injection. There was some visualisation of the arterial tree, and the first cerebral arteriogram in the living was obtained. However the patient developed severe post-procedure symptoms and unfortunately died, partly thought to be due to the carotid ligation and strength of the contrast. The death was a great shock to the team and Moniz wrote 'This accident, the only one we had in the course of our early investigations before arriving at the desired conclusion, was a great shock to us. We thought much about it, but considering the films obtained, we gave heed to the opinion of some competent colleagues to the effect that we should continue, though more cautiously, the experiments we had begun. They gave us their valuable support.'

Moniz further wrote 'The main idea in our work to obtain cerebral arteriography as the following. With a precise picture of the normal arrangement of the cerebral arteries made opaque to X-rays, we thought it would be possible to make the diagnosis of the localization of the majority of tumours through the alteration in the normal arterial pattern in the cerebrum. Many tumours, or at least the very vascular ones, should also show their own circulation.'

There was about a month of indecision and it was decided to use a new group of substances opaque to X-rays, the iodides. After these techniques failed he tried using intra-arterial injections using an iodide salt. Moniz chose iodine because of its higher atomic weight compared to bromine. The team again made preliminary experiments using iodides of ammonium, sodium, potassium, and rubidium. For patient studies a 25% solution of sodium iodide was used and the effect of dilution and arterial capacity were determined. It was felt that 5ml would be enough. In two patients injections of 3ml of 25% sodium iodide were made with limited success. In the third patient an intra carotid injection with a temporary ligature was made using the rapid injection of 5ml of 25% sodium iodide. The injection was successful with arterial filling and their positions were altered due to the presence of an intracranial tumour. His successful patient, on 28th June 1927, was the ninth in his series, a young man with a pituitary tumour. Moniz wrote and published describing the new technique in detail. The head had to be held still for angiography (fig 21), and figure 22 shows a typical labeled angiogram and using Thorotrast as a contrast medium.

Following the successful patient there was a period of development of the technique, including the use of stereoscopic angiography, and a deepening of the understanding of the appearances [46]. Perhaps not unsurprisingly the cerebral arteriograms and subsequent venograms revealed anatomy that differed from classical descriptions and therefore supported Morton's prediction.
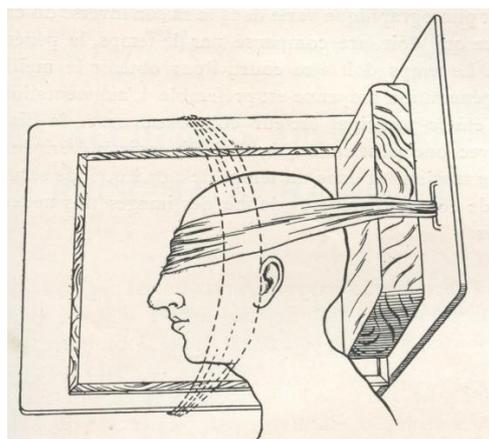
Fig. 21 Positioning of the head for cerebral angiography, from Moniz (1931).
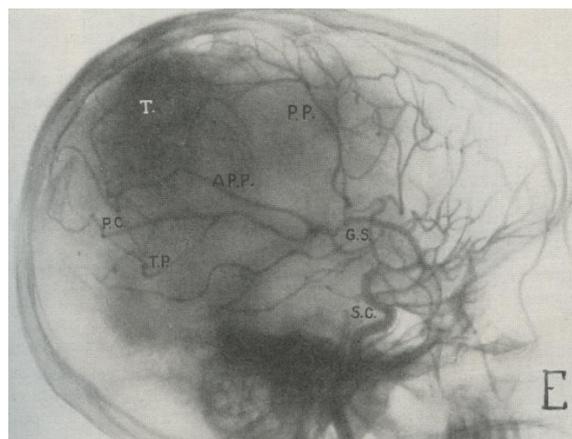

Fig. 22 Cerebral angiography with the vessels labelled, from Moniz (1931). T is tumour.

In 1929 Moniz's surgical colleague Reynaldo dos Santos, Professor of Surgery in Lisbon, introduced percutaneous Trans Lumbar Aortography (TLA) by direct aortic puncture with injection of a sodium iodide solution. Dos Santos described the technique [47]. Punctures were made into the aorta with a long needle in a variety of positions including above the coeliac trunk, above the kidneys, above the inferior mesenteric artery and above the origin of the common iliac artery (fig 23). Figures 24 shows abnormal vascularity in a sigmoid tumour in a TLA performed by dos Santos, and also note the stationary grid lines. The contrast used was a 100% solution of pure sodium iodide, which was quite toxic. The injection was painful and therefore required anaesthesia. The TLA became the standard vascular examination for decades and was being routinely performed over 50 years after the procedure was first described. There were surprisingly few complications from the procedure. The examination illustrated (fig 25) was performed in 1982.
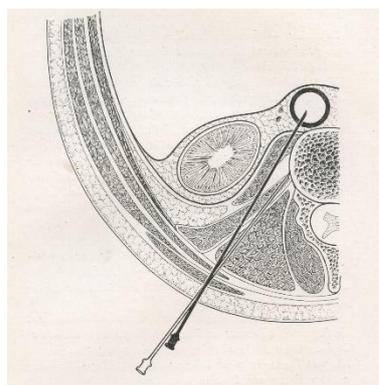

Fig. 23 The technique of trans-lumbar aortography, from Dos Santos (1932).
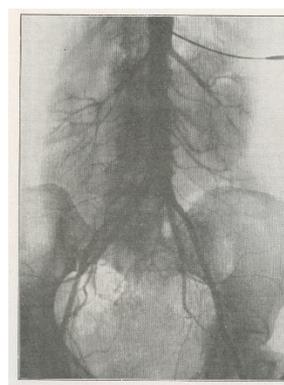

Fig. 24 A TLA for a sigmoid tumour showing abnormal vascularity. Note the stationary grid lines. From Dos Santos (1932).

Other members of Moniz's team ware equally innovative and successfully introduced angiopneumography (that is pulmonary angiography) by de Carvalho [48], lymphography by Monteiro, phlebography (that is venography) by Joäo Cid des Santos who was the son of Reynaldo, and portal venography by Pereira. It was in 1929 Werner Forssmann had introduced a well-oiled ureteral catheter via an antecubital vein into his own right atrium, and it was in 1931 that Moniz, de Carvalho and Almeida Lima using the Forssmann method demonstrated the pulmonary vasculature with an injection of sodium iodide. The Portuguese School therefore introduced many aspects of clinical angiography in the 1930 to 1950 period but the international adoption of their techniques was severely delayed by the Second World War.

VI.6. Thorotrast in Angiography and its Consequences.

In 1931 Thorotrast was introduced as a contrast medium and in the October was first used in cerebral angiography. The new contrast medium was seen as a great improvement since it was not irritant and gave an excellent opacity. In 1950 Almedia Lima described Thorotrast and compared its use favourably to the organic iodine derivatives used at the time [49]. Thorotrast was a colloidal suspension of thorium dioxide, being a stable aqueous colloidal solution containing 25% thorium

dioxide by volume in a tapioca-dextrin medium. A preservative of 0.15% methyl p-hydroxybenxoate was added to the solution. Lima wished for a better contrast medium however felt that at that time none was available. Lima knew of no other substance that gave such satisfactory results as Thorotrast. He had not seen any serious disturbances following its use and had personally performed 2,000 angiograms. He saw the problems related to local tissue reactions and the fact that it was not eliminated from the body. He therefore recommended the abandonment of its use for ventriculography and encephalography. Of all myelographic agents Thorotrast was found to be the most irritant to the pia-arachnoid resulting in both systemic and local reactions. The local reactions caused a severe arachnoiditis and a cauda-equina syndrome.

Problems could arise following the local injection of Thorotrast with extravasation and the development of a local reaction and mass, the so-called Thorotrastoma (fig 26) [50]. Thorotrast was retained in the walls of the vessels and histology showed little balls of Thorotrast in the branches of small cerebral vessels. However the main danger lay in the permanent retention of a radioactive substance in the body (fig 27). Thorotrast conglomerates emitted radiation as part of the decay of thorium 232. The majority of the radiation was α-radiation and β and γ-radiation contributed less than 10% to the total dose. Somewhat surprisingly Almedia Lima concluded as late as 1950 that 'the tissue alterations and the radioactivity of Thorotrast are of no importance in the dosage of this substance as used in angiography,' and he recommend angiography with Thorotrast (20% colloidal suspension of thorium dioxide) with a dose of 8ml to either side. Unfortunately Lima's optimism was to prove unfounded, partly as a result on the work of Hermann Muth and the German Thorotrast Study [51]. Thorotrast was in use in Germany from 1929 to 1955, and the first quantitative biophysical studies to determine the activity concentrations of radionuclides derived from the naturally occurring thorium series were undertaken in Germany from 1946 to 1949. The dose estimates were of such concern that production of Thorotrast was stopped, and it was withdrawn from the market in 1949 to 1950. This makes it all the more curious that Lima was recommending its use in 1950. A detailed German Thorotrast Study started in 1968 and reported after 20 years in 1988. The results were interesting [52]. The study found an excess rate of various neoplasms including malignant liver tumours, myeloid leukaemia, and tumours of bile ducts, pancreas, oesophagus and larynx. The Thorotrast patients had a statistically significant loss of lifetime as a function of the dose rate, and this could not be accounted for purely by the known Thorotrast specific diseases. The Study concluded that the long-term irradiation of the reticuloendothelial system not only resulted in an excess death rate of certain neoplasms, but that there was also an acceleration of the manifestation of other illnesses leading to premature death.
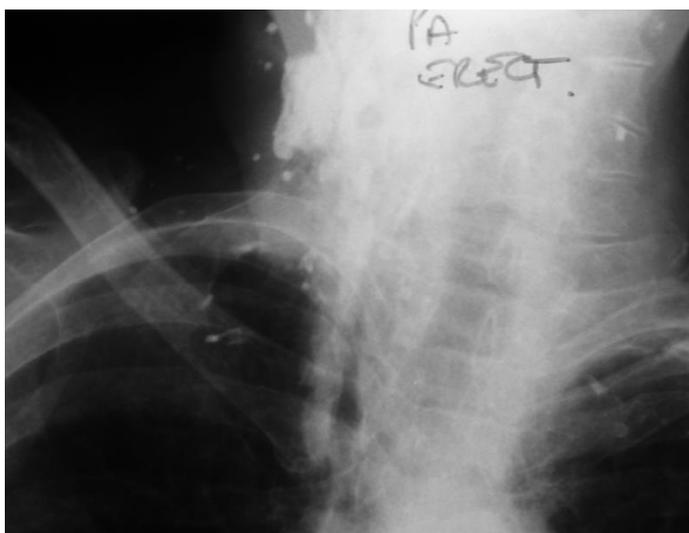

Fig.25 Trans Lumbar Aortogram, 1982.

Fig.26 A Thorotrastoma shown as dense shadowing on the right side of the neck

VI.7. The Seldinger Technique and the development of Catheter Angiography.

A major development related to the method of delivery of contrast medium into vessels and the heart chambers was achieved by Sven Seldinger in 1956, working at the Karolinska Clinic in Stockholm [53]. He introduced the needle-guidewire-catheter replacement technique which permits selective catheterisation and injection of most arteries, veins and cardiac chambers of the body from a simple femoral arterial or venous puncture. This technique is fully established as the optimum method of visualising any important artery including the carotid, vertebral, coronary, renal and mesenteric arteries and for cardiac catheterisation and selective angiocardiography. This catheter technique, aided by the low osmolar contrast agents permits virtually painless, safe arteriographic visualisation of any arterial or venous territory or cardiac chamber, so

revolutionising diagnostic imaging. This extremely versatile percutaneous catheterisation technique has been very successfully developed to introduce therapeutic equipment, so permitting angioplasty, vessel occlusion, atherectomy etc., introducing the modern era of intravascular interventional therapy. It is noteworthy that just as the techniques for catheter angiography for diagnosis were perfected that they were swept away by newer and non-invasive techniques including ultrasound and cross-sectional imaging. Vascular access is now almost completely used for interventional procedures.

VII. NEURORADIOLOGY

VII.1. Ventriculography, encephalography and air myelography.

There had been several case reports of patients surviving with intracranial air. One such case was described by Sebastian Gilbert Scott in 1915, showing spontaneous pneumocephaly in a woman who complained of her brain splashing (fig 28). Walter Dandy from Johns Hopkins Hospital was aware of such instances, and also of the value of the appearances of abnormal gas collections to diagnose abdominal disease. In 1918 Dandy described ventriculography followed by encephalography in 1919. In the latter procedure, air is injected by lumbar puncture in order to fill the ventricular system. Dandy also predicted the development of air myelography for spinal lesions, and subsequently this was performed by Jacobaeus from Stockholm who demonstrated three spinal tumours in 1921. There were disadvantages to air myelography. Since gas did not mix with the cerebro-spinal fluid the fluid needed to be removed and replaced with gas. This resulted in significant post myelography headaches. However air, or the more rapidly absorbed oxygen, was the least irritating of all myelographic agents. Unfortunately the contrast produced using air was relatively poor, even when combined with tomography, and overlying gas filled organs caused confusing images. In the 1960s gas myelography was still occasionally performed, and survived into the CT era as air meatography when a small quantity of gas was used to outline the acoustic nerve in the internal auditory canal before the universal use of magnetic resonance imaging (MRI).

Fig.27 Thorotrast seen as densities in the liver, in a shrunken spleen, and centrally in lymphatic tissue.

Fig.28 Air in head, a patient of Sebastian Gilbert Scott (1915).

Encephalography was not easy to perform, and at the first International Congress of Radiology held in London in 1925, JW Pierson, who was a colleague of Dandy, said that the procedure was dangerous and complicated, but in favour said that in competent hands it should not be nearly so dangerous as exploratory craniotomy and could give more information. Dandy had only three deaths in a series of 500 examinations. Following the description of ventriculography by Dandy in 1918, the neurosurgeon Harvey Cushing reproached him for spoiling the intellectual challenge of deducing the site of the brain lesion from the history and physical examination. Currently the issue is reversed, and it has been quipped that the patient is now referred to the neurologist when the CT or MRI scan is normal!

VII.2. Myelographic agents

VII.2.i. Lipiodol.

Jean Sicard and Jacques Forestier had been using epidural injections of Lipiodol to treat sciatica and had injected it intrathecally without obvious harm [54]. They described its use in intra-arachnoid, intramuscular, intravenous, intratracheal, and oral locations. They were able to demonstrate the subarachnoid space in health (fig 29) and in the presence of disease including tumours (fig 30). Lipiodol is a viscid, halogenated, poppy seed oil containing 40% iodine as an organic combination. It was a light yellow colour and slowly turned brown due to the release of free iodine. It did not mix with the spinal fluid and was only absorbed slowly. It was viscous which made removal difficult and tended to break up into globules. Lipiodol was irritant and could cause a late painful arachnoiditis.

Fig.29 The normal subarachnoid space shown with Lipiodol, which was injected into cisterna magna and allowed to flow own into the lover spine. From Sicard & Forestier (1928).
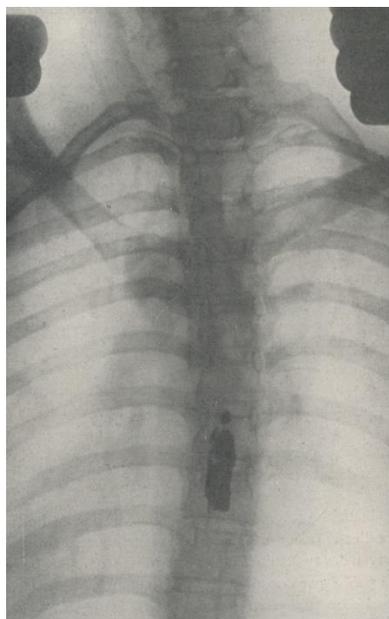

Fig.30 An intradural tumour with subarachnoid space injection of Lipiodol into the cisterna magna. The movement of the contrast is blocked by the tumour. From Sicard & Forestier (1928).

Lipiodol was used in many areas, including gynaecological (fig 31), and was a versatile agent. Lipiodol ultrafluid was used for lymphangiography in the 1980s until the procedure became obsolete, and was also used for sialography.

VII.2.ii. Myodil (Pantopaque).

Lipiodol was used for myelography until iopendylate (Pantopaque or Myodil) was introduced in the 1940s. Iopendylate was not water-soluble and was absorbed only slowly. There was again a small risk of adhesive arachnoiditis following its use. Pantopaque is a mixture of ethyl esters of isomeric iodopentyllundecyclic acids containing 30.5% of firmly bound organic iodine. Similar to Lipiodol the solution became discoloured on exposure to light due to the release of free iodine and needed to be discarded. Pantopaque was less viscous than Lipiodol and so had less of a tendency to break up into globules and was easier to remove. Pantopaque had reactions including meningitis and a delayed arachnoiditis. Robert Shapiro writing in 1968 said 'All in all, Pantopaque is an eminently satisfactory medium for most problems in the spinal canal, with a low incidence of untoward reactions' [55]. In addition to myelography Myodil was used for ventriculography, and had also been introduced into the amniotic sac to outline the foetus prior to intra-uterine blood transfusion.

The practice in the UK was to use a smaller quantity of Myodil for myelography and to aspirate it after the procedure, which is part of the reason for the lower incidence of adhesive arachnoiditis in the UK. If the Myodil was left in place then there would be a prolonged elevation of the serum iodine.

The topic of informed consent of patients before radiological procedures is important. By the 1990s it was good practice to discuss possible side effects and complications with the patient before a radiological procedure but this did not apply during the period of Myodil use. It was generally believed, somewhat paternalistically, that a patient should not be worried unnecessarily by an overemphasis on side effects since they might then refuse a procedure that the doctor believed would be in their best interests.

VII.2.iii. Water Soluble Agents

Before 1970, only iodinated oils including Myodil (Pantopaque) were available for myelography. Ionic compounds were generally considered too toxic although occasionally they were used for lumbosacral radiculography.

The possibility of using Conray was considered. Conray is sodium iothalamate mixed with a methyl meglumine salt, however it produced severe local reactions in several patients and could not be recommended. The advances were made in the 1970s when the ionic water soluble Dimer X was introduced in 1972, and the non-ionic metrizamide in 1977.

The French company Guerbet developed the ionic compound meglumine iocarmate (Dimer-X), combining two tri-iodinated benzene rings into one large molecule (hence it was a dimer) containing six atoms of iodine and so reducing the osmolality. Dimer-X could only be used in the lower portions of the spinal canal below the spinal cord for radiculography but it produced superb quality radiographs of the lumbosacral nerve roots. Though much less toxic than the previous aqueous contrast media, it had to be used with great care and in a strictly limited dosage. By contrast, metrizamide could be used throughout the spinal canal and was much less toxic than meglumine iocarmate, which it replaced for myelography and radiculography in the late 1970s. The images obtained were elegant and beautiful (fig 32). Initially metrizamide was limited in use to the thoracolumbar region, and until 1980 a special licence was needed from the Department of Health to examine the basal cisterns. The water-soluble agents showed the nerve root sheaths better and so Myodil was gradually abandoned.
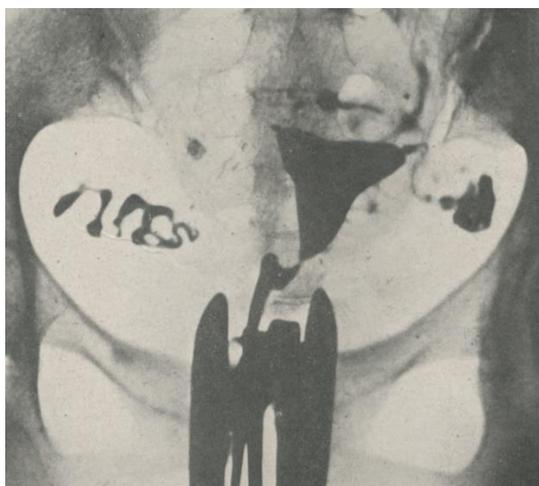

Fig.31 Lipiodol hysterosalpingography, with filling of the uterine cavity and Fallopian tubes, from Sicard & Forestier (1928).

Fig.32 A lumbar radiculogram using metrizamide. The lower spinal cord and nerve roots (cauda equina) are shown beautifully.

VIII. BRONCHOGRAPHY.

The bronchial tree could be opacified with an opaque medium using a variety of techniques. The first experimental bronchogram was performed by Karl Springer from Prague in 1906, which is surprisingly early. In the illustration (fig 33) a catheter was used with contrast injected. The examination shows a normal right bronchogram. The examination was unpleasant for the patient and there was therefore a high threshold of referral for performing the examination. The chest physician would be reluctant to submit the patient for the procedure unless there was a degree of confidence about the examination. The introduction of high resolution computed tomography (HRCT) has considerably changed attitudes to bronchiectasis. Since so many more patients are investigated than was possible with bronchography it is now known that bronchiectasis is very much more common than had previously been appreciated. Over the years many contrast agents were used in the bronchial tree, including colloidal silver and bismuth. In the classical technique Dionosil was introduced by direct tracheal injection or was dripped over the back of the tongue. It could also introduced using a catheter, or a bronchoscope. It was used not only to diagnosis bronchiectasis, but also to investigate lung tumours, cysts and abscesses in the time before fibreoptic bronchoscopy and CT scanning.

Dionosil (propyliodone) was a contrast agent allied to diodone in a firm organic combination to prevent it breaking down to iodides or to free iodine. The aqueous form was a 50% aqueous suspension, and the oily form was a 60% suspension in arachis oil.

IX. INTERSTITIAL AIR STUDIES

A gas used as a negative contrast medium could be introduced into the tissues by direct injection. Examples include retroperitoneal air studies and pneumo-mammography.

IX.1.i. Retroperitoneal Air Studies.

In this technique the retro peritoneum around the kidney is outlined by gas. Paul Rosenstein from Berlin and Humberto Carelli from Buenos Aires both described the technique independently in 1921. A 10cm needle was used to make a retroperitoneal injection directly. Rosenstein injected 600ml of oxygen and Carelli injected about 200-400 ml of carbon dioxide. The examination was introduced in the days before the IVU to show the kidney. Rosenstein emphasised that it was 'important that the radiologist became independent of the clinician for these pictures.' Rosenstein said that this technique was of value in:

- Determining the presence of one or both kidneys. Removal of a solitary kidney would be a disaster.
- Determining the size of a kidney.
- Showing the presence of kidney stones more clearly.
- Looking for displacements of kidneys. This would diagnose the 'floating kidney' which was thought to be a cause of symptoms as a part of visceroptosis.
- Diagnosis of renal tumours and tumours around the kidney.
- To study 'acute stresses' of the kidney. In unexplained renal colic the enlarged pelvis could be shown outlined by gas.

In later years the technique was combined with tomography and was primarily used to show the adrenal glands. The examination illustrated was performed in 1943 by Rohan Williams by direct retroperitoneal interstitial injection (fig 34).

Fig.33 Normal right bronchogram. The branching bronchial tree is shown beautifully. The central dense line is the opaque catheter used for injection.

Fig.34 Retroperitoneal air study. The injecting needle is seen and the kidney is outlined by gas.

IX.1.ii. Presacral Perirenal Pneumography.

 A variant of the technique was presacral perirenal pneumography. This was reviewed by John Laws in 1958 and it was then almost exclusively used to visualize the adrenal glands [56]. The gas, when injected in front of the sacrum, passes up in the retroperitoneum and outlines both kidneys and adrenal glands. Laws   believed that the technique he described and used

was safe and avoided the risk of gas embolism. Laws described the use of pure oxygen on the grounds that its greater solubility in serum makes the risk of inadvertent intravascular injection less serious. The use of carbon dioxide was also described. Carbon dioxide is more than 20 times more soluble in serum than oxygen, and up to 100 ml of carbon dioxide as a gas may be injected intravenously with no serious effects. The preferred gas for presacral injection was therefore carbon dioxide and the quick absorption meant that the procedure caused the patient discomfort for only a short period of time, with the whole examination including the taking of films being completed in approximately 30 minutes.

IX.2. Pneumo-mammography/Roentgen Pneumastasia.

The injection of gas into the breast was proposed by Alberto Baraldi in Argentina in 1933. He initially injected purified air into the anterior and posterior regions of the breast producing emphysema. He further developed the technique by the use of oxygen which was better absorbed. He described the technique as absolutely innocuous, and with minimal symptoms. The gas was injected into three areas, being retromammary, retropectoral and subcutaneous. The technique would show masses within the breast, or evidence of chest wall invasion. Figure 35 shows a later examination using carbon dioxide, with a fibroadenoma demonstrated. Gas might also be injected into a cyst following aspiration of the fluid contents and followed by mammography to assess the cyst contents in the period before ultras0und.

Contrast studies of the ductal system of the breast were also performed using a wide variety of agents, including Thorotrast, bismuth, lipiodol, sodium iodide, air, and iodinated water soluble contrast agents. These studies were performed to investigate bloodstained discharges.

X. Diagnostic pneumoperitoneum/gynaecography.

In the technique of pneumogynaecography an abdominal radiograph is made following the induction of a pneumoperitoneum. The technique was first developed by Eugen Weber from Kiev in 1912. A specifically gynaecological use was described by Otto Goetze from Halle in 1918. Following the induction of a pneumoperitoneum the patient was placed head down and prone, and a pelvic radiograph was obtained with the pelvic viscera clearly outlined with air. The bowel would fall out of the pelvis, and the uterus, bladder and ovaries could be identified. Goetze said that he used the technique to diagnose pregnancy in the early months, infantilism, myomata, uterine and adnexal adhesions, pyosalpinx and ovarian tumours. The technique was reviewed by Marchesi and others in 1955 [57]. The authors used between 1500 and 2000 ml of gas. The outlines of the uterus and ovaries were demonstrated in this examination, however like most contrast studies there is no indication of internal structure. Marchesi was able to show some internal structure by combining gynaecography with hysterosalpingography (fig 36), that is by using a negative contrast medium around the uterus and by filling the uterus with a positive contrast medium.
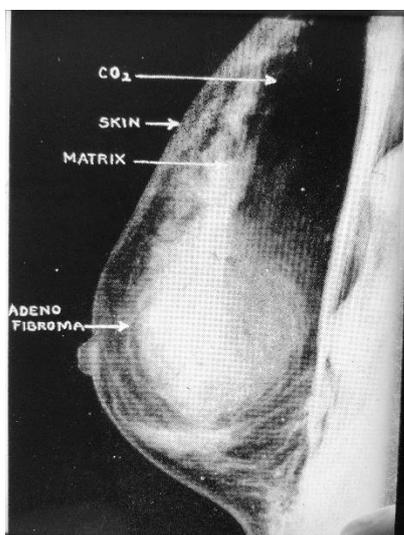

Fig.35 Pneumo-mammography/Roentgen Pneumastasia. The central mass, a fibroadenoma, is outlined with the carbon dioxide injected into the breast.

Fig.36 Gynaecography combined with hysterosalpinography – normal examination, From Marchesi (1955)

The patient illustrated (fig 37) was examined in 1967 and the examination was normal. This examination was performed before the introduction of ultrasound, which rendered the examination obsolete.

The technique of pneumoperitoneum is now routinely used with the introduction of intraperitoneal air prior to laparoscopy, or aqueous iodinated contrast may be injected to outline the peritoneal space in the diagnosis of hernia, although this latter technique has been replaced by MRI.
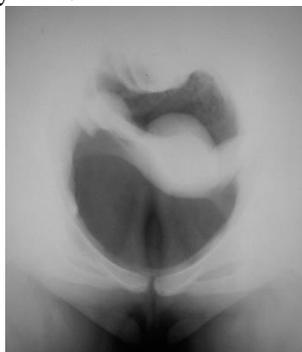

Fig.37 Gynaecography in 1967 – normal examination. The pelvic organs are seen clearly outlined by gas.

XI. Discussion

In the years since November 8, 1895 when Röntgen   discovered X-rays in his laboratory at Würzburg, there have been major developments in all aspects of medical imaging, and many undreamt of by the pioneers. In the forefront has been the synthesis of safer, more effective, more physiological, lower osmolar water soluble iodinated contrast media, and methods for their delivery [58] . This sequential development has fully realised the most optimistic dreams of Cameron, Binz, Räth, Swick, Wallingford, Hoppe, Almén and the many other researchers.

Many of the examinations that are described in this paper are invasive and are not without complications. However it should be noted that these examinations were best practice for their time. Even a relatively short time ago, what for us today would be a simple question to answer, could be surprisingly difficult to answer and would require   an invasive diagnostic procedure. The traditional paradigm of medical care commonly involved invasive diagnostic procedures which were followed by invasive therapy. Modern medicine has replaced this with the model of non-invasive diagnosis and minimally invasive therapy. Medical practice continuously changes and advances are sequentially made, and an advance in one area may facilitate a change in another [59]. The development of safe contrast media had facilitated this change. So successful have been these new imaging technologies, that ultrasound systems and magnetic resonance angiography can produce excellent vessel demonstration with additional data on blood flow. Most of the conventional contrast medium examinations are now largely obsolete, however the newer agents have a firm place in interventional minimally invasive procedures [60].

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MEDICAL PHYSICS DEVELOPMENT IN AFRICA – STATUS, EDUCATION, CHALLENGES, FUTURE

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I. INTRODUCTION AND 10 YEARS OF FAMPO

Formation of FAMPO

At the 48th Annual South African Association of Physicists in Medicine and Biology (SAAPMB) meeting in Durban (South Africa) in 2008, the idea of establishing an African regional body of medical physics was mooted by the then IOMP Vice-President, Prof. Fridjtof Nuesslin. A letter of intent was prepared to the IOMP executive committee, after which a draft constitution was developed. The draft constitution was unveiled in March 2009. The first Executive Committee of FAMPO was elected at the African Radiation Oncology Group (AFROG) conference in Harare (Zimbabwe) in December 2009, with Ahmed ibn Seddik (Morocco) elected as President and Rebecca Nakatude (Uganda) as Vice-President. Other elected members were Khaled El-Shahat (Egypt) and Taofeeq Ige as Treasurer and Secretary-General respectively. In March 2010, the IOMP council approved FAMPO's application as the newest and youngest regional organization of the International Organization for Medical Physics (IOMP). As part of FAMPO 10th Anniversary celebrations, the IOMP Journal Medical Physics International made its issue of Dec 2019 focused on medical physics development in Africa [MPI, 2019].

Aims and Functions

FAMPO was established to improve and solve the challenges faced by Medical Physicists in Africa and with aims and functions as follows: (i) To promote improved quality service to patients and the community in the region (ii) To promote the co-operation and communication between medical physics organization in the region, and where such organizations do not exist between individual medical physicists (iii) To promote the profession and practice of medical physics and related activities in the