CONTRAST MEDIA
FOR RADIOLOGICAL EXAMINATION
IN GASTROINTESTINAL TRACT
LEAKAGE.

An experimental and clinical study

Radiologische contrastmiddelen bij gastro-intestinale lekkage.
Een experimenteel en klinisch onderzoek.

PROEFSCHRIFT

door

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PROMOTIECOMMISSIE

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From inability to let well alone:
from too much zeal for the new
and contempt for what is old:
from putting knowledge before wisdom,
science before art, and cleverness before
common sense,
from treating patients as cases, and from
making the cure of the disease more
grievous than the endurance of the same,
Good Lord, deliver us.

<div style="text-align: center">Sir Robert Hutchinson</div>

To Javaid
   Samina and Nasra

To the memory of
   my father and my mother.

CONTENTS

Abbreviations:
CM : Contrast media
GIT : Gastrointestinal tract
UGIT: Upper gastrointestinal tract

Introduction and aim

Radiological contrast media are essentially drugs introduced in the body with one and only one desired effect - attenuation of radiation, thereby making the blood vessels, parenchymal or hollow viscera visible radiographically. All other effects or side effects of contrast media are basically undesirable or unwanted (Almen, 1983). The aim of the present study has been to find a safe and suitable contrast medium for radiological evaluation in patients with leakage or perforation from the gastrointestinal tract (GIT). The experimental work was triggered by a few serious untoward reactions occuring after contrast medium examinations for suspected leakage from the GIT. Fatalities due to such use have also been described in the literature (Ansell, 1968; Chiu and Gambach, 1974).

Leakage from the gastrointestinal tract, regardless of its cause, can take place into the mediastinum, the pleural or peritoneal cavity or into the bronchi or lungs either by fistula formation or aspiration. The contrast medium (CM) used for the evaluation of leakage should be expected to have the following properties:

— The CM should be adequately radiopaque for visualization of the leakage.
— The CM should not give rise to either acute or delayed, local or systemic toxic reactions in case of leakage to the bronchi or lungs, mediastinum, pleura or peritoneum.
— In case of leakage, the CM should either absorb easily into the circulation or be removable.
— The CM should be palatable for the patient when given orally.

In order to find the safest contrast medium, experimental studies were carried out on the bronchi and lungs, mediastinum, peritoneum and pleura of rats using the following contrast media:

1) "Pure" barium sulphate suspension. — 90% weight/volume (w/v)
2) (Micropaque®) — Commercial barium sulphate suspension 100% w/v (Laboratories Nicholas Gaillard).
3) (Gastrografin®) — Sodium and Meglumine Diatrizoate 370 mg I/ml (Schering, Berlin).
4) (Dionosil®) — Aqueous suspension of N-propylester of 3:5-diiodo-4-oxopyridin-1-ylacetate (Glaxo Laboratories Ltd, Greenford Middlesex).
5) (Hytrast®) — Aqueous suspension of N-propyl-2:3 diol 3:5-diiodo-4-pyridone (NPP) and 3:5 diiodo-4-pyridone (DIP) (Guerbet Laboratories, Paris)
6) (Amipaque®)* — Metrizamide in a concentration of 370 mg I/ml (Nyegaard Company, Oslo)
7) (Hexabrix®) — Meglumine and sodium ioxaglate 320 mg I/ml (Laboratories André Guerbet, Paris)

* In the experimental study on the pleura Omnipaque® (iohexol 350 mg I/ml, Nycomed, Oslo) was used in place of Amipaque.

On the basis of the experimental results, a clinical study has also been carried out.
Chapters 2 and 3 are devoted to the description of the various contrast media. The aetiology of leakage and choice of contrast media for radiological evaluation along with the experimental design and clinical experiences are discussed in chapter 4.
The various parts of the experimental work are described in detail in chapters 5, 6, 7, 8 and 9. The clinical study is presented in chapter 10. Chapter 11 consists of general discussion and conclusions and is followed by a summary.

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Barium sulphate as contrast medium

A. Historical aspects

In order to trace the history of the invention of gastrointestinal contrast media, it would perhaps not be out of place to remind ourselves that X-rays were first discovered in 1895 by Wilhelm Conrad Roentgen in Germany. The discovery of this specific type of radiation had a very deep influence on science and particularly on the practice of medicine. It opened up for physicians a diagnostic opportunity which had never before been possible, the ability to see organs without actually opening up the patient.

In the early days only bones and metallic objects could be recognized by X-rays, but it was within a few months of Roentgen's discovery that a search for some method to visualize the soft tissues and internal organs started. Experiments were carried out by passing metallic instruments in cadavers to make the oesophagus visible on fluoroscopy. Strauss (1896) in Germany tried capsules of iron oxide and bismuth subnitrate in the oesophagus. Hemmeter (1896) in the same year in the United States introduced capsules of reduced iron and rubber bags containing lead solution into the stomach of living individuals. These methods, however, did not prove to be very practical.

Cannon and Moser (1896) were the first to use capsules of bismuth subnitrate and later bismuth mixed with bread meals and demonstrated to the American Physiological Society the use of these contrast media in the fluoroscopic study of the mechanism of swallowing in a goose. Rumpel (1897) in Germany and Roux and Balthazard (1897) in France also tried to use bismuth subnitrate for fluoroscopic demonstration of oesophagus and stomach.

It is surprising to note that Cannon as early as 1897 had selected barium and bismuth as the two most likely contrast substances for the gastrointestinal tract, because of their high radio-opacity.

Rieder (1904) was the first to describe the method of bismuth meal examination in 1903. Many changes have been made since then, both in the technique of the stomach examination as well as the contrast medium used. Bismuth was used initially instead of barium because it was a registered product. Bismuth preparations were however associated with many toxic effects, often due to the presence of impurities, which were difficult to remove.

The first use of barium was described in 1904. In 1910 Bechem and Gunther proposed the use of barium sulphate because it was cheaper and could be purified to a greater degree than bismuth. The contrast medium studies were first carried out on the upper gastrointestinal tract (UGIT). Small bowel and colon examinations were started some time after the UGIT studies. Schüle was the first one to perform a radio-opaque enema of the colon in 1904. It was however in 1911 that Haenisch described the fluoroscopic contrast medium examination of the colon. The interest in the small bowel examination was greatly enhanced by the description of regional enteritis by Crohn and his associates in 1932. It is however noteworthy that there have been tremendous refinements in the method of use and the physical properties of barium sulphate preparations since those early days.

Gas has been introduced as a contrast medium and combined with barium sulphate to produce the modern double contrast examination particularly of oesophagus, stomach, duodenum and colon.

Air insufflation to produce a double contrast examination of colon was first carried out in 1921 by Laurett of Sweden. Fischer of Frankfurt in 1923 developed and popularized the basic method, which is still used today for double contrast examination of the colon. Starting with very humble beginnings at the turn of the last century, gastrointestinal radiology has now come a very long way.

The hard work of those earlier masters of science, which paved the way for the tremendous achievements in the field of roentgen diagnosis should however not be forgotten.

B. Barium sulphate suspension

Barium sulphate is a heavy insoluble material produced from barite. It has a specific gravity of 4.5. Its molecular weight is 233.4. For ease and understanding we can consider barium sulphate in two forms:
— "Pure" barium sulphate (without any additives)
— "Commercial" barium sulphate (with additives)

"Pure" barium sulphate:

The so called "pure" barium sulphate suspension is barium sulphate powder suspended in water containing no other substances or additives. It flocculates readily within the stomach and intestines. It produces very poor mucosal coating and therefore even large lesions may be missed when a pure barium sulphate suspension is used.

"Commercial" barium sulphate:

The so called "commercial" barium sulphate preparations such as Micropaque consist of a barium sulphate suspension with the addition of small amounts of other substances called additives. These additives or adjuvants are used with the purpose of improving the suspension, miscibility, taste and mucosal coating properties of barium preparations. A very large number of additives have been described in the literature and different commercial preparations contain a few additives specific to the particular brand of barium sulphate. Miller & Skucas (1977) have given a list of 90 different additives and according to these authors the list is not even comprehensive. The exact type and proportions of the additives used are very often kept a secret by the manufacturers of barium sulphate suspensions.

C. Standardization

Standardization is necessary for relatively accurate mixing of barium sulphate suspensions. The two well known systems used are the weight/weight (wt/wt) and the weight/volume (wt/vol) percentage systems. An example of wt/vol system is 20 Gms of barium sulphate mixed with enough water to make 100 ml of final suspension. This is a 20% wt/vol suspension. If 20 Gms of barium sulphate powder is mixed with 80 Gms of water to make 86.3 ml of final suspension then this is a 20% wt/wt suspension. The amount of barium may be the same in the above mentioned preparations but the specific gravity, density and the amount of final suspension is quite different.

D. Mucosal coating

Mucosal coating can be described as a fine film of barium sulphate sticking to and coating the mucosa of the gastrointestinal tract.

Cracking, fragmentation, peeling, flaking and clumping are various terms used to describe disintegration of the mucosal coating. Some properties of barium sulphate which affect mucosal coating are:

Particle size and shape: Barium sulphate is a white crystalline powder consisting of rhombic crystals, which form aggregates. All barium sulphate contrast media contain these aggregates in varying sizes and shapes. All barium sulphate suspensions, which are opaque always have particles larger than colloidal size range (per definition "suspensions" have particles greater than 0.1 μm, "colloidal solutions" have particles under 0.1 μm and over 0.001 μm and "true solutions" have particles under 0.001 μm in mean diameter). The variable large particle size of the barium sulphate suspensions is of major importance for showing fine details of stomach mucosa.

For any given weight of barium sulphate the surface area requiring a given amount of water adsorption in order to wet its surface increases geometrically with reduction in particle size. Therefore reduction in particle size results in increase

in viscosity and reduction in fluidity due to preferential adsorption of water over a large surface area (Revill, 1971).

Settling: Settling or sedimentation of barium sulphate can take place both in vitro and vivo. Barium sulphate suspensions however vary considerably in the way and the time they take to settle down depending on the suspending agents and additives they contain. A barium sulphate suspension which settles down quickly can cause layering in the stomach, small bowel or colon, thereby hiding possible lesions and is therefore unsuitable for radiological examination.

When barium sulphate is suspended in a liquid, it settles under the influence of gravity according to Stokes' Law, which states that "the settling rate decreases rapidly with a decrease in particle size or an increase in the viscosity of the suspending medium or both" (Revill, 1971). Suspensions in which the particle size is larger than 0.1 μm will settle after standing a long time. Particles below 0.1 μm, ranging from 0.01 μm - 0.1 μm, will not settle for extremely long periods of time. In practice, however, the barium suspension used for examination of the oesophagus and stomach have a large number of particles in the range 1.0 μm - 20.0 μm.

The large particle size is in fact very important to enhance the density of barium sulphate suspensions and obtaining the excellant mucosal pattern of areae gastricae in the stomach and mucosal detail in the oesophagus. Because of their large particle size these suspensions would settle fairly quickly and form a cake at the bottom, which is not easy to resuspend when left for several hours. This is the reason why the high density (200 - 250% wt/vol) preparations, such as E.Z.E.M. high density barium sulphate 250% wt/vol, are usually obtainable only in powder form for suspension just before use.

Flocculation: Negatively charged suspensions are precipitated by positive ions and positively charged suspensions are precipitated by negative ions. The neutralized particles agglomerate in a process called flocculation. In the stomach the complex acid and mucous contents and in small intestines succuss entericus, pancreatic and bile secretions in variable quantities in different individuals may result in clumping and flocculation of barium. Efforts are therefore made by manufacturers of barium sulphate suspensions to overcome the flocculation problems by adding extremely small amounts of protective colloid additives. Their chief function is to protect the barium particles from electrolytes and other adsorbed substances. In coating the particle and restraining particle-to-particle contact these additives help to stop flocculation. However since so many variables are involved a perfect solution to this problem is not yet available (Miller and Skucas, 1977).

Foam and bubbles: These influence the mucosal coating

and therefore can cause inaccuracies in the diagnosis. Foaming and bubbles should therefore be minimized in an ideal preparation. Various types of additives are added to the barium sulphate suspension which act as anti-foaming agents, but other factors such as the hardness and temperature of water used also influence foaming and bubble formation.

Advantages and disadvantages of barium sulphate in the GIT

Reviewing the literature (Lessman and Lilienfield, 1958; Cochran et al, 1963; Almond et al, 1961; Miller and Skucas, 1977; Cohen et al, 1980; Grobmyer et al, 1984) and from personal experience one can state that barium sulphate suspensions have the following advantages and disadvantages.

Advantages:
1. Good delineation and X-ray visualization due to high density.
2. Due to addition of suspending agents and other additives to barium sulphate, it does not precipitate or flocculate quickly. This makes it an excellent contrast medium for examinatation of the intact gastrointestinal tube.
3. Can be given without fear to dehydrated patients as it is not hyperosmolar.
4. Low cost.

Disadvantages:
1. Barium Sulphate may inspissate above a large bowel obstruction.
2. Prolonged follow through studies are often not possible due to tendency of barium sulphate to flocculate with time.
3. Since it is not water-soluble and therefore not miscible with blood and body fluids barium sulphate is contra-indicated in any perforation or suspicion of leakage outside the GIT.
4. When leaked outside the gastrointestinal tube into the peritoneal cavity barium sulphate is not absorbed and can give rise to fatal peritonitis or lead to granuloma formation, fibrous reaction and adhesions. These adhesions can later produce serious sequele such as intestinal obstruction and death.
5. Mediastinitis may occur due to the leakage of barium sulphate into the mediastinum.
6. In the lung barium sulphate has been known to cause necrotizing bronchopneumonia.
7. The effects of barium sulphate on the pleura are not known.

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Iodine containing contrast media

I. Water-soluble contrast media

A. History and evolution of water-soluble contrast media

It was in 1923 that Osborne a venereologist in the Mayo Clinic first noticed that urine in the bladder was opaque on X-ray films in some of his syphilitic patients treated with large doses of sodium iodide. Sodium iodide was, however far too toxic for radiological purposes. In 1925-1926 Binz, professor of chemistry and his assistant Rath synthesized organic iodine preparations of pyridine in Berlin in search for improved treatment for syphilis and other bacterial diseases. Binz and Rath synthesized some 700 pyridine compounds, some containing arsenic and iodine. This series contained about 73 preparations, which contained iodine and were excreted in substantial amounts by kidney and liver. Binz sent these preparations to various medical colleagues in Europe to try them for their effectiveness in kidney and gallbladder infections. Swick (1929) in Berlin, showed great interest in trying one of these pyridine compounds containing iodine as a diagnostic rather than a therapeutic agent. Uroselectan was selected from Binz's preparations with which Swick in 1929 produced the first reliable urogram. This discovery changed the whole field of urology and opened up the field of angiography (Grainger, 1982).

By 1931 two other contrast media containing 2 atoms of iodine in the pyridine ring were introduced (Diodone and Iodoxyl) by Binz and Rath. These products stayed as the radiological vascular contrast media of choice for more than 20 years.

The six carbon benzine ring was replaced for pyridine ring as the carrier for iodine in sodium acetrizoate which was introduced to clinical radiology in 1952 by Hoppe (1956) and was produced by Sterling-Winthrop and other companies (1956-1959).

Sodium diatrizoate (Urografin and Hypaque, later Gastrografin) (Fig. 1a, 2b) was introduced in 1954 and the immediate derivatives, such as iothalamate (Conray), metrizoate (Isopaque, Triosil) are the standard contrast media used routinely for urography, angiography and many other purposes for over 30 years now. All these CM are **ionic** monomeric salts of tri-iodinated substituted benzoic acids and are referred to as **conventional** water-soluble contrast media.

These ionic monometric contrast media are highly hypertonic. They have an osmolality, which is 5 to 8 times that of human plasma and other body fluids. The osmolality of any solution is dependent on the number of particles per molecule of the solute. These conventional water-soluble media ie., the sodium or meglumine salts of monomeric tri-iodinated substitued benzoic acids, dissociate in solution, each molecule producing an iodinated anion (containing 3 iodine atoms) and a non-radiopaque cation (sodium or meglumine). These salts are therefore ratio 3:2 media (3 atoms of iodine to 2 particles per molecule). It is noteworthy that the cations form 50% of the particles in solution in the ionic CM and therefore also contribute to 50% of the final osmolality of the contrast solution, but are not radiopaque.

The most important advance in contrast media synthesis came in 1968, when Almen (1969) in Sweden introduced the concept of nonionic media. The objective for the introduction of the non-ionic compounds was to retain the high iodine content of contrast media solution which is necessary for adequate radio-opacity, but reduce the osmolality by eliminating the radiographically useless cations ie., sodium or meglumine. **Non-ionic** contrast medium metrizamide (Amipaque, Fig. 1b, 2d), also called the **first generation** of low osmolality contrast media, was brought to the market in 1972 by Nyegaard & Co., Oslo. Being nonionic, metrizamide does not dissociate in solution and is a ratio 3:1 substance (3 iodine atoms to 1 particle per molecule). The osmolality of the nonionic media is therefore theoretically, 50% that of the ionic monomeric media. Amipaque has however the considerable disadvantage of not being able to be sterilized by autoclaving. It is therefore manufactured in freeze-dried form and needs to be prepared into solution just before use.

Modifications of the metrizamide formula by substituting different side chains has resulted in the production of **second generation** of low osmolality products such as iopamidol (Niopam, Bracco, Milan) and iohexol (Omnipaque; Nycomed, Oslo), which are stable in solution and can be autoclaved and marketed as sterile solutions for direct use (Grainger, 1982). Hexabrix or ioxaglate is the third member of the second generation of low-osmolality contrast media. It is a two-to-one mixture of meglumine and sodium salts of ioxaglic acid (Fig. 1c, 2c). Hexabrix is an ionic compound but contains two benzine rings each containing 3 atoms of iodine, linked by a bridge to form one large molecule. Similar to the non-ionic compounds

(Amipaque, Omnipaque) Hexabrix is also a ratio 6:2 or 3:1 medium (6 atoms of iodine to 2 particles in solution). It has therefore also theoretically half the osmolality of conventional contrast media, at similar iodine concentrations (see also table I for comparative data of different CM as regards osmolality, particle ratio and LD 50).

Table 1.

Data extrapolated from Recent Advances in contrast media by Michal A. Bettmann and Thomas W. Morris (1986).

Medium	Type	● Ratio	■ LD50 (Gms/Kg)	▲ Osmolality (m.osmol/Kg.)
Ionic				
Diatrizoate	Monomer	1.5	7.5	1570
Ioxaglate	Dimer	3.0	13.4	560
Non-ionic				
Metrizamide	Monomer	3.0	18.6	480
Iohexol	Monomer	3.0	24.2	690
Iopamidol	Monomer	3.0	22.1	616
Iotrol	Dimer	6.0	26.0	360

● Ratio $\dfrac{\text{no. of iodine atoms}}{\text{no. of dissolved particles}}$

■ The acute median lethal dose in mice

▲ Osmolality at 300 mgms I/ml.

B. Some terms and definitions commonly used

Concentration

Both ionic and nonionic contrast media are supplied in a range of different concentrations, in other words in different iodine concentrations eg., omnipaque is available as 240 mgm I/ml or 350 mgm I/ml solutions and the individual properties of these solutions eg., viscosity and osmolality vary with the difference in iodine concentration.

Viscosity

In contrast media, viscosity, is a function of the shape, number and charge of the soluble particles as well as the viscosity of the solvent. Viscosity influences the ease with which contrast solution can be drawn into a syringe and injected by hand. The viscosity of contrast media solution can be recuded simply by warming the ampule or bottle in a water bath to physiological temperature of 37°C. (Dawson et al., 1983). A low viscosity contrast medium is needed for vascular use for easy and quick administration of relatively large quantities. For gastrointestinal use this is not an important factor and somewhat higher viscosity is of no disadvantage for such examinations.

Osmolality

The osmolality of a contrast solution or any solution depends on the number of particles per molecule of the solute.

The osmotic pressure of an aqueous solution is defined as 'a force that must be applied to counterbalance the force arising from the flow of water across a semipermeable membrane' (Lehringer, 1975).

C. Conventional water-soluble contrast media used in the G.I.T.

Gastrografin (ionic monomer)

Canada in 1955 first introduced the use of water-soluble contrast media for examination of the GIT. Due to the hyperosmolality of these media, their use became controversial soon afterwards in 1956. Many reports in favour of and against these media have been published in the literature. In 1958 Lessman and Lilienfield published a study on the use of Gastrografin and advocated its use in the GIT. Gastrografin is a hypertonic water-soluble contrast medium containing sodium and meglumine diatrizoate. It also contains small quantities (0.1%) of tween 80 as a wetting agent and anise as a flavouring agent. It has a high osmolality of ± 1900 m. osmols/Kgm water, which is about 6 times that of plasma and other body fluids (± 300 m. osmols/Kgm water). It has been used since 1958 in the radiological evaluation of the gastrointestinal tract in patients in whom there could be a contraindication to the use of barium sulphate.

D. Advantages and disadvantages of Gastrografin in the G.I.T.

Review of the literature (Lessman and Lilienfield, 1958; Ansell, 1968; Chiu and Gambach, 1974; Harris et al, 1964; Rowe et al, 1971; Rowe et al, 1973; Miller and Skucas, 1977; Frech et al, 1970; Wagget et al, 1970; Lutzger and Factor, 1976; Johansen and Kolmannskog, 1978; Margulis, 1983) and from personal experience it would appear that Gastrografin has the following advantages and disadvantages.

Advantages:
1. Gastrografin has adequate density for demonstration of gross abnormalities in certain parts of the GIT.
2. Gastrografin is water-soluble and miscible with blood and body fluids, therefore would be completely absorbed in case of leakage outside the GIT.
3. Due to its hyperosmolality Gastrografin is suggested to be used in the management of newborn babies with meconium ileus and meconium plug syndrome.

Disadvantages:
1. The hyperosmolality of Gastrografin is associated with the following dangers:
   a. Gastrografin, in case of aspiration or leakage to the

lungs, can cause severe pulmonary oedema, which can be fatal.

b. Following oral use Gastrografin presents itself to the capillary membrane of the bowel wall as an osmotic force. The amount of fluid passing across such a semi-permeable membrane as bowel mucosa depends on the surface area of the membrane, osmotic gradiant and the time of surface contact. Since Gastrografin has 6 times the osmolality of blood there is a clear shift of fluid from the blood capillaries in the bowel wall into the bowel lumen. This would lead to a decrease in circulating plasma volume, which can prove hazardous and has been known to cause serious metabolic disturbances with possible danger of death in babies. Such a hazard is of course also obvious in ill, debilitated adult patients and those with pre-existing dehydration.

c. Gastrografin when administered orally may also lead to increase in blood osmolality. This is attributed to absorption of some of the contrast medium through the bowel wall. Rowe (1973) has shown experimentally that there was a disproportionate rise in the measured osmolality as compared to the calculated osmolality of blood, when Gastrografin was administered experimentally to puppies. This suggests a significant absorption of the contrast material or its components through the intact gut wall. The hyperosmolality of blood appears therefore, to be caused be a combination of contrast agent absorption and plasma volume decrease.

2. Due to its hypertonicity, Gastrografin induces hyperperistalsis, when used orally, which gives rise to diarrhoea, which is undesirable.

3. Solidification of gastrografin was reported by Hugh et al. (1970) which resulted in impaction of a Sengstaken - Blakemore balloon, when gastrografin within it was solidified due to acid absorption through the balloon membrane.

4. Gastrografin has been known to precipitate in the stomach due to the presence of acid in the stomach.

5. Lutzger and coworkers (1976) have shown that gastrografin causes severe inflammatory reaction when used experimentally for enema in the colon of animals. According to these authors neither the osmolality nor the methylglucamine diatrizoate itself is responsible for this toxic effect and they have suggested that the additive, Tween 80 used in gastrografin may be responsible for these toxic, irritating effects on the bowel mucosa.

E. Lower osmolality contrast media for use in the G.I.T.

These newer lower osmolality contrast media have not yet been used widely in the gastrointestinal tract, but due to their lower osmolality they would appear to be more suitable

than the conventional contrast media.
— Amipaque (non-ionic monomer)
— Omnipaque (non-ionic monomer)
— Hexabrix (ionic dimer)

Amipaque, Omnipaque and other monomeric non-ionic media such as Niopam have a similar basic chemical formula with one tri-iodinated substituted benzine ring, with an amide group replacing the carboxyl group of the conventional ionic salt (see Fig. 1b). These are ratio 3:1 (Fig. 2d) substances and therefore have theoretically half the osmolality of conventional ionic media (Fig. 2b).

Hexabrix (sodium and meglumine ioxaglate).
Hexabrix was produced by combining two tri-iodinated benzine rings in order to have six iodine atoms in the contrast molecule. Each benzine ring has initially a carboxylic acid (-COOH) group. One such group (-COOH) is converted to a non-ionising radical and the other -COOH group is converted to an ionising salt (sodium or meglumine). This chemical structure is called a mono-acid dimer. Mono-acid; because it has one carboxyl group, dimer; because it contains two benzine rings (Dawson et al., 1983). Hexabrix 320 has an osmolality of 580 m.osmols/Kg water with a 1:2 ratio between sodium ioxaglate and methylglucamine ioxaglate. It is also a ratio 3:1 contrast medium (Fig. 1c, 2c) as it has 6 iodine atoms and two particles in solution (6:2 = 3:1) and has therefore theoretically half the osmolality of conventional ionic media such as diatrizoate.

In practice the osmolality of the nonionic media and Hexabrix is even less than half that of ionic media for the same iodine content due to aggregation of some of the particles thereby reducing further the number of particles in solution. The osmolality of Hexabrix and nonionic monomers such as Amipaque and Omnipaque is in fact about ⅓rd that of conventional ionic media with the same iodine concentration (Grainger, 1980).

F. Advantages and disadvantages of lower osmolality contrast media in the G.I.T.

On reviewing the literature (Johansen, 1978; Johansen and Kolmannskog, 1978; Cohen et al, 1980) and from personal experience the newer lower osmolality contrast media would appear to have the following advantages and disadvantages when used in the GIT.

Advantages:
1. Adequate radio-opacity for radiographic visualization.
2. Amipaque, Omnipaque and Hexabrix due to their lower osmolality (which is ½ to ⅓rd of the conventional contrast media), when aspirated into the lung are not expected to lead to pulmonary oedema.
3. If leakage occurs into mediastinum, pleura and

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peritoneum, these contrast media being water-soluble and miscible with blood and body fluids, are expected to be completely resorbed.

4. Due to the lower osmolality these CM are not diluted in the small bowel, therefore it is possible to carry out a follow through examination with an adequately high contrast density in the bowel.

5. Due to their lower osmolality these contrast media are not expected to cause fluid shifts, when administered orally, therefore, particularly useful in small children and sick and debilitated adults.

Disadvantages:

1. Amipaque has the disadvantage of instability in aqueous solution, which necessitates its production as a dry powder, which needs to be reconstituted just before use. Amipaque has for practical purposes been replaced by other very similar non-ionic media, which are stable in solution. Examples of these so called second generation of non-ionic media are Omnipaque (iohexol) and Niopam (iopamidol).

2. Higher cost of all the newer lower osmolality contrast media is a relative disadvantage.

G. Summary of important features of water-soluble (primarily intravascular) contrast media (Almen, 1983)

— Contrast media are essentially drugs introduced in the body with one and only one desired effect - attenuation of radiation and thereby making the blood vessels, parenchymal or hollow viscera visible radiographically. All other effects or side-effects of contrast media are basically undesirable or unwanted.

— High water solubility at high iodine concentration is a desirable property.

— Low osmolality which is as close as possible to body fluids, is an advantage.

— Low viscosity is generally desirable for intravascular use.

— Chemical stability of contrast medium is important so that the contrast agent can be dispensed in a ready to use fluid form.

— Biological safety is essential.

— Before a contrast medium is administered to a patient it is not known which patho-physiological mechanism or which combination of different mechanisms happen to be the greatest risk for that particular patient on that special occasion.

— Increase of contrast media dose increases the frequency and/or severity of adverse effects both in animals and in patients.

— There are similar adverse contrast media effects in animals and in man.

— The cost of contrast media may well be an important deciding factor in their use.

Future contrast media

Since search goes on for even better CM with higher iodine concentrations and lower osmolality, nonionic dimers (Fig. 1d, 2e) containing six iodine atoms for every dissolved molecule achieve an iodine/particle ratio of 6/1 = 6. These compounds, although essentially isotonic with blood at 300 mgI/ml have a high viscosity, which until now makes them unsuitable for wide clinical use (Sovak, 1982).

A high cost of production might also be a determining factor in the use of the non-ionic dimers, when they come into the market. They may however, in time become the future media of choice in the gastrointestinal tract radiology in cases where use of water-soluble contrast media is indicated.

diatrizoic acid

a

metrizamide

b

ioxaglic acid

c
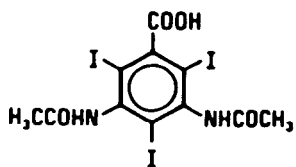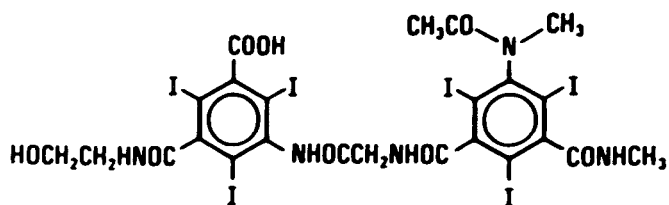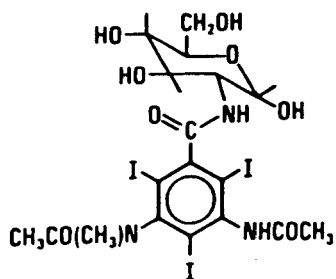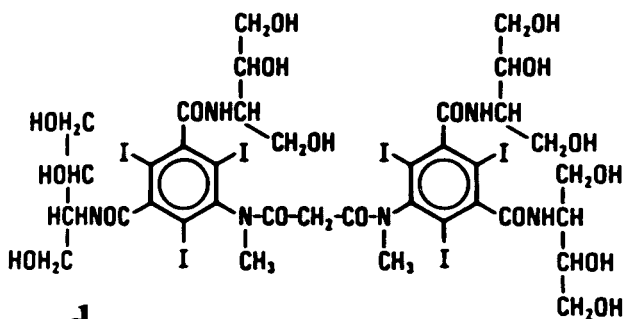
iotrol

d

Fig. 1 Chemical formulae of:
a. Diatrizoic acid (ionic monomeric contrast medium eg., Gastrografin)
b. Metrizamide (Amipaque which is a non-ionic monomeric contrast medium)
c. Ioxaglic acid (Hexabrix which is a ionic dimer)
d. Iotrol (This is an example of future dimeric non-ionic contrast media)

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Fig. 2   Simple presentation of chemical structure and evolution of various water-soluble iodine containing contrast media and the ratio of iodine atoms to number of dissolved particles in solution. The ratio directly relates to osmolality, the higher the ratio, the lower the osmolality of the contrast medium.

a. Sodium iodide, the earliest iodine containing CM.
b. Conventional monomeric ionic CM (Gastrografin).
c. Lower osmolality ionic dimeric CM (Hexabrix).
d. Lower osmolality non-ionic monomeric CM (Amipaque, Omnipaque or Iopamidol).
e. Nonionic dimeric CM (future CM such as Iotrol).

II. Oil or water suspensions of iodinated contrast media

A. Bronchographic contrast media

Iodinated oils were introduced as contrast media, mainly for bronchography, by Sicard and Forestier in 1922. These contrast media consisted of a vegetable oil in close chemical combination with iodine eg., Lipiodol which contained poppy seed oil. These iodinated oils gave excellent radiographic contrast and were only slightly irritating but suffered the disadvantages of easy alveolar filling (due to their low viscosity) and retention in the lungs for long periods of time. They also caused delayed inflammatory reactions in the lungs with granuloma formation and sometimes acute and delayed reactions to iodine which led to almost complete abandonment of these contrast media. Due to these disadvantages of oily CM water-soluble iodine compound were also tried for bronchography as early as 1931 by Lenarduzzi and Olper. Due to the quick absorption and dilution of the hypertonic water-soluble compounds it was not very easy to obtain good quality bronchograms. To delay the absorption, various substances were used to thicken the contrast medium. Morales and Heiwinkel (1948) described experiments and clinical studies with iodopyracet (diethanolamine salt of 3,5-diiodopyridine-N-acetic acid) combined with carboxymethyl cellulose (CMC). These compounds also became unpopular due to the significant irritating effects in the lung and the inability to obtain good quality bronchograms due to rapid absorption of the CM. The solution to the problems was found by Tomich et al. (1953) who postulated that an iodine compound, which was only slightly soluble in body fluids and hence slowly eliminated, would be needed. This would help to overcome the disadvantages of the iodinated oils which were too slowly eliminated and the water-soluble CM which were too quickly diluted and eliminated. This finally led to the production of Dionosil as a bronchographic contrast medium in 1952. Hytrast was introduced much later in 1962.

Dionosil (Aqueous and Oily)

Tomich and his co-investigators (1953) introduced Dionosil for bronchography in 1952.
Dionosil (Glaxo laboratories, Ltd. Greenford, Middlesex, London) has the following formula, and is available in two forms, Dionosil oily and Dionosil aqueous: N-propylester of 3:5-diiodo-4-oxopyridin-1-ylacetate.
Dionosil oily is a 60% wt/vol opaque suspension of crystals (5-14μm range) in pure arachis oil. Dionosil aqueous is a 50% wt/vol. opaque suspension of the crystals in water with carboxymethyl cellulose (CMC). Sodium citrate is present as a buffer and sodium chloride renders the preparation isotonic. A small portion of benzyl alcohol is added as a

bacteriostatic agent (House, 1977). The physical properties of these suspensions are shown in the table below:

The physical properties of Dionosil, aqueous and oily: (Rayl and Spjut, 1963).

Property	Dionosil aqueous	Dionosil oily
Viscosity (centipoise)	$\pm$ 1200	$\pm$ 1250
Specific gravity (atroic)	1.27	1.26
PH	$\pm$ 7.0	not applicable
Iodine % w/v	28.4	34.1
Surface tension (dynes per cm²)	41.0	32.5

Ten to 20 ml of contrast medium per adult lung may be used for bronchography. The aqueous suspension is considered to give a better bronchial coating although it is somewhat more irritating to the mucosa (Walker and Ma, 1971). Alveolar filling is known to occur more commonly with the oily prepration, particularly if larger quantities of contrast medium are used for bronchography (Joynt and Harnick, 1955).
The alveolar filling is a disadvantage as the contrast medium which enters the alveoli is likely to be retained in the lungs. The contrast medium retained in the lung produces a mild to moderate transitory acute inflammatory reaction of a foreign body type (Dunbar et al., 1959). Granuloma formation has also been demonstrated by some workers (Björk and Lodin, 1957). Pulmonary fibrosis has not been shown by the use of this contrast medium (Johnson et al., 1960).
Dionosil aqueous and oily, are certainly an improvement on the previous oily media such as Lipiodol due to a more even coating of the bronchi for diagnostic accuracy. There are very few clinical symptoms such as pneumonia after the use of these contrast media for bronchography, and there is virtually no risk of chronic inflammatory reaction.

Hytrast

Introduced by Gildenhorn et al., in 1962 (Gildenhorn et al., 1962). The opaque white suspension is obtained by the dispersion of a mixture of fine crystals (size 2.5 μm) of two iodine compounds. N-propyl-2:3 diol 3:5-diiodo-4-pyridone (NPP) and 3:5-diiodo-4-pyridone (DIP) in a slightly hypotonic aqueous solution of CMC. Hytrast produced in France (Lab. André Guerbet, Paris) has the following formula (Grainger, 1970):
— iopydol 46 Gms.
— iopydone 30.5 Gms.
— methyl and propyl hydroxybenzoates 0.07 Gms.
— sodium carboxymethyl cellulose 1.5 Gms.
— distilled water to 100 ml.
This Hytrast prepration has a viscosity of 6 poises at 37°C.

Hytrast manufactured in America (L.V. low viscosity) (E. Fougera and Co., Hicksville, Long Island, N.Y., U.S.A.) has the same formula with only one difference ie., the sodium carboxymethyl cellulose content is reduced to 0.5%. This reduces the viscosity of the American preparation to 2.4 poises at 37°C. compared to the French preparation (6 poises at 37°C.). The combined iodine wt/vol is 50%. It is however more irritating to the lung than Dionosil (Rayl and Spjut, 1964). Alveolar filling may also take place more easily with lower viscosity preparations. The crystalline, Hytrast, which is retained in the alveoli may be eventually phagocytosed and removed by macrophages via the bronchi or lymphatics (Wright, 1965). The retained crystals however, may initiate a significant inflammatory reaction (Rayl and Spjut, 1963, 1964) and a crystalline pneumonia is fairly common in areas of contrast retension (Cabrera et al., 1967). Deaths have also been reported in the literature due to the use of Hytrast (Agee and Shires, 1965).

B. Advantages and disadvantages of bronchographic contrast media in the G.I.T.

The review of the literature (Dunbar et al., 1959; Johnson, 1960; Rayl and Spjut, 1963; Cabrera et al., 1967; Agee and Shires, 1965) leads one to expect the following advantages and disadvantages of Hytrast and Dionosil when used in the GIT.

Advantages:
1. Adequate radio-opacity for demonstration of leakage.
2. If leakage occurs to the bronchi and lungs, these contrast media could be considered relatively safe as they are not hyperosmolar and are in any case the CM normally used for bronchography.

Disadvantages:
1. Oil based contrast media tend to form globules, which is not desirable for the GIT examination.
2. Hytrast appears to give significant toxic reactions in the lungs, therefore would not be suitable in case of leakage to the lungs.
3. High viscosity of these bronchographic contrast media may be a disadvantage for demonstration of fine leaks which may be missed.
4. No information is available as to their safety in case of leakage to mediastinum, pleural or peritoneal cavity.

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Leakage from the gastrointestinal tract

A. Aetiology of leakage

Leakage from the gastrointestinal tract lumen can take place due to a variety of causes. To name all the possible causes of leakage is beyond the scope of the present study. A patient for example with a perforated stomach or duodenal ulcer, a perforated colonic diverticulum, a rupture of the appendix, a perforation associated with Crohn's disease or carcinoma may present as an acute emergency. In these situations the diagnosis is often made on clinical grounds and plain views of the abdomen or thorax are taken showing free air outside the lumen of the GIT as a sign of perforation. Contrast studies are not always possible in these patients. Some of the "leakages and perforations" which come to the attention of the radiologist for diagnosis may be briefly described according to the region involved as follows:
— upper gastrointestinal tract
— small bowel and colon

Upper gastrointestinal tract

The oesophageal leakages will be described in somewhat more detail as major oesophagus surgery is very frequently undertaken in this hospital which therefore, also provides more personal experience in this region of the GIT.

— Ematogenic injury of oesophagus
— Endoscopic perforation
— Postoperative anastomotic leaks

Ematogenic injury of oesophagus

a. Mallory-Weiss syndrome.

Upper gastrointestinal haemorrhage precipitated by violent vomiting in Mallory-Weiss syndrome, was described by two workers in 1929 and 1932 and therefore is named after them. The anatomic lesions of Mallory-Weiss syndrome consist of radial tears only involving the mucosa and submucosa in the area of the oesophagogastric junction. Most patients are males (Michel et al, 1980) and 85% vomit red blood. The patient has often ingested considerable amounts of alcohol and sometimes acetylsalicytic acid (Kanauer, 1976).

b. "Spontaneous" rupture of oesophagus

The first description of the so called 'spontaneous" perforation of the oesophagus was published in 1724 by Hermann Boerhaave. In his treatise titled "History of a Grieveous Disease Not Previously Described", he recorded the clinical and morphological details of the case of Baron John van Wassenaar, Grand Admiral of the Netherlands (cited in Rogers et al., 1972).

Spontaneous pneumomediastinum and Boerhaave's syndrome may occur as a result of vomiting and the precursors common to both may be coughing, status asthmaticus, childbirth, weightlifting, defecation and epileptic seizure and rarely even a forceful swallowing. However in one series of 47 patients 11 patients gave no history of vomiting (Abbott et al., 1970) and in another series 4 out of 11 patients gave no history of vomiting (Bradley et al., 1981). No underlying disease of the oesophagus is detected in these cases of spontaneous rupture of oesophagus. The sequence of events leading to rupture have been suggested to be as follows: (Rogers et al., 1972; Kinsella et al., 1948; Brownstein, 1969; Ware et al., 1952): The basic mechanism of rupture is considered to be hydrostatic. Fluid is placed under tension within the oesophagus, exceeding the tensile strength of the oesophageal wall resulting in perforation. There is moderate to marked gastric distension and very often there is a history of overindulgence in food or drink or both. The intragastric pressure is raised, which may be accomplished by vomiting. There is relaxation of distal oesophageal sphincter which allows the gastric contents to enter and distend the oesophagus, but at the same time there is a failure of relaxation of the proximal oesophageal sphincter, which results in further increase in oesophageal distension and an increase in intraluminal pressure.

The most common (90%) site of rupture of the oesophagus is the left posterolateral wall of the oesophagus and is variably described as being 2 - 6 cm proximal to the oesophagogastric junction and usually consists of a linear vertical rupture 1.5 - 4 cm in length, involving all layers of the oesophagus. The diagnosis needs to be made early for a successful and immediate surgical treatment. A chest X-ray and contrast oesophagogram is absolutely essential for an immediate diagnosis. The oesophagogram should be positive in a large majority of cases and when negative (in case of persisting clinical suspicion), a repeat oesophagogram may be indicated.

Endoscopic perforation

a. Oesophagus

The frequent use of upper gastrointestinal fiberoptic endoscopy has led to an increase in the number of

perforations. Oesophageal perforation is 4 times as common as gastric or duodenal perforation and can occur during diagnostic or therapeutic endoscopic procedures (Chung, 1985). The region of the hypopharynx and proximal oesophagus, at the cricopharyngeous is the most frequent location as this is the narrowest region. Rarely perforation occurs in an unsuspected Zenker's diverticulum, which is entered preferentially in the course of a blind insertion of the endoscope (Chung, 1985). Perforations of the lower oesophagus are much less common since the arrival of the flexible endoscopes. The mortality rate from endoscopic procedures is 1 - 2 per 10.000 procedures and is mostly due to perforation (Mandelstam et al., 1976).

A 1974 survey by the Amercian Society of gastrointestinal endoscopy of 211410 oesophagogastroduodenoscopic examinations showed a perforation rate of 0.13% (Silvis et al., 1976). Dilatation of oesophagus, for example, for strictures resulting from reflux oesophagitis, lye ingestion, postoperative stenosis and achalasia carries a definite increased risk of perforation. The removal of foreign bodies such as dentures, bones or pull tabs of aluminum cans from the oesophagus also carries a very large risk of associated perforation of the oesophagus.

Intubations eg., with Celestin and other similar prosthetic tubes in oesophagus can also cause iatrogenic perforations. Endotracheal tubes, nasogastric or oral feeding or suction catheters can also rarely cause oesophageal injuries (Wolff et al., 1973).

b. Stomach and Duodenum

Perforation of stomach by endoscopy is rare now-a-days, but a blowout of a recently sealed perforated ulcer may occur due to air distension (Chung et al., 1981). Rarely electrocoalgulation employed for polypectomy or to stop beelding may lead to full thickness necrosis of the wall of stomach and a deep biopsy of a malignant ulcer may cause perforation. Rupture of the duodenum occurs most commonly opposite the superior duodenal angle (Chung, 1985).

Perforations below the diaphragm present clinically with pain and tenderness of the abdomen, which persists longer than expected (several hours) after the endoscopic examination. Plain chest radiography and contrast medium examinations are required for confirmation of the diagnosis, when not recognized at the time of endoscopy. Most of these patients require a surgical exploration and suturing of the rent.

Postoperative (anastomotic) leak

a. Oesophagus

There have been significant improvements in the techniques used in the GIT operations in the last two decades. This means an increased number of advanced anastomotic operations are undertaken. The radiological examinations are also more frequently required to evaluate postoperative complications, such as a possible anastomotic leak. The clinical presentation of anastomotic leak varies. It may be manifested by one or a combination of signs eg. persisting fever, tachycardia, cardiac arrhythmias related to mediastinitis, persistant atelectases, persistant or recurrent pleural effusions, empyema, prolonged ileus, subphrenic abscess and wound-infections (Fromm, 1985).

The presentation of the leak depends on its magnitude and stage of recognition. The mortality associated with anastomotic leaks is described as above 80% in some series (Hermreck and Crawford, 1976).

It however appears that most series have not distinguished between "free" leaks and "contained" leaks. The outcome of a "free" leak is obviously more serious than that of a "contained" leak. Immediate diagnosis is essential in order to start the appropriate treatment. Radiographic reassessment is often required after several weeks and before starting oral feeding in these patients.

Anastomotic leaks may be suspected in patients with any type of reconstructional surgery on oesophagus eg. colonic, gastric or jejunal interposition; free intestinal graft or skin flap reconstruction in place of cervical oesophagus and hypopharynx.

Other surgical procedures on oesophagus and pharynx which may be associated with leakage include:
— repair of congenital tracheo-bronchial fistulae
— oesophageal myotomy for lower oesophageal achalasia
— myotomy for cricopharyngeal dysphagia and Zenker's diverticulum
— operations of epiphrenic diverticula, such as excision and myotomy
— antireflux operations eg., Nissen fundoplication.
— various surgical procedures on the larynx and pharynx.

Leakage from surgery on oesophagus and pharynx may involve:
— Mediastinum and soft tissues of the neck: a small leak from the oesophagus can permit air to escape into soft tissues of the neck; mediastinum, chest and abdominal wall and travel retro-peritoneally. Leakage of oesophageal contents can lead to severe mediastinitis or abscess formation in the soft tissues, which may sometimes lead to an oesophago-cutaneous fistula.
— Pleura: A leakage from the oesophagus, in particular from the lower oesophagus, can easily extend to the pleural space. This can happen in cases of reconstructional surgery or after hiatus hernia repair. An oesophago-pleural fistula may also arise after pneumonectomy.
— Lungs, trachea and bronchi: These may be injured during surgery which may lead to oesophago-tracheal or oesophago-bronchial fistula. Aspiration with its associated risks is quite common postoperatively.
— Peritoneum: a tear in the lower oesophagus or leakage

from an anastomosis in the upper abdomen, such as oesophagojejunal anstomosis may give rise to peritonitis or localized abscess formation such as subphrenic abscess.

b. Stomach and duodenum.

Anastomotic leaks may arise after operations for ulcer disease or malignancy. There is very little difference in the incidence of anastomotic leaks from Billroth I and Billroth II anastomosis. However disruption of the duodenal stump suture line occurs more commonly than the gastrojejuno-stomy suture line of a Billroth II reconstruction. This occurs in 2-3% of Billroth II gastrectomies with a 40-80% mortality rate (Pearson et al., 1963).

The clinical presentation of suture line disruption can be difficult to distinguish from acute pancreatitis, therefore an early radiological assessment with a suitable contrast medium is essential in these cases.

The management of the patient depends on the extent and type of leakage ie., free peritoneal leak or a contained leak. The former usually demanding a reoperation and the latter is often treated conservatively (Fromm, 1985).

Gastric perforation can occur postoperatively after gastric bypass procedures undertaken for obesity. The most common causes of leakage are anastomotic leaks, leaks through disrupted staple lines, necrosis as a result of loss of blood supply, distension of distal stomach as a result of pylorospasm, operative injury and even pressure necrosis from nasogastric tube. Anastomotic leaks after gastric bypass procedures have been reported in as many as 4-5% of the patients and are most common around 3-6 days after surgery (Ackerman et al., 1985).

Small bowel and colon
— Colonoscopic perforation
— Postoperative (anastomotic) leak

Colonoscopic perforation

The incidence of colonoscopic perforations is much higher than upper GIT endoscopic perforations. The 1974 United States GIT endoscopy survey in a very large series of endoscopies puts the rate of perforation at 2/1000 (in a total of 25298 colonoscopies) for diagnostic colonoscopy and 3/1000 for colonoscopic polypectomies (in a total of 6214 polypectomies) (Silvis et al., 1976). Perforations most commonly occur following the use of electro- or photo-coagulation. A deep biopsy may sometimes result in perforation.

In a doubtful clinical situation an erect chest X-ray (for free air under the diaphragm) and a contrast examination would help to reach a diagnosis before an emergency laparotomy.

Postoperative (anastomotic) leak

a. Small bowel
Many types of operations including bypass procedures, resections and anastomoses are performed on the small bowel in such conditions as benign or malignant tumours, intussusception, Crohn's disease, obstruction or Meckels's diverticulum. A postoperative anastomotic leak would need a thorough clinical and in certain cases radiological assessment.

b. Colon
Colon resections may be undertaken for inflammatory bowel diseases such as ulcerative colitis or Crohn's disease or for diverticular disease, or colorectal malignancy. Suture line disruption can occur between seventh and ninth post-operative day. Early recognition of this complication is essential to minimize mortality and morbidity. The incidence of anastomotic disruption is highest after low anterior anastomosis. An anastomotic leak incidence of 25-50% is reported with contrast enema (Golicher et al., 1970). One-half to one-third of the disruptions, however, are contained (or pocketed) leaks communicating with the rectum lumen or bowel lumen and would generally require no specific therapy. Free leak would however need to be treated as intra-abdominal rupture. Generalized peritonitis occurs from free peritoneal leak due to any underlying cause and needs immediate exploration. A radiological assessment may be required in a case where clinical diagnosis is unclear.

B. Choice of contrast media for radiological evaluation of GIT leakage

Summary of literature study: (for references see section on advantages and disadvantages of different CM):

The following points can be made on the basis of the study of the literature regarding which contrast medium to use in case of leakage.

1. Most authors prohibit the use of barium sulphate in any suspicion of GIT leakage.
2. Most authors advocate the use of water-soluble contrast medium Gastrografin for radiological evaluation of leakage from the GIT.
3. Some authors advocate the use of barium sulphate in place of Gastrografin in order to avoid the possibility of pulmonary oedema caused by possible aspiration of Gastrografin in oesophagus examinations.
4. The use of hypertonic Gastrografin has been considered hazardous by some authors in the gastrointestinal tract particularly in small children and debilitated and dehydrated adults.
5. Some authors have suggested that pure barium sulphate (without additives) may be less toxic and cause less granuloma formation and adhesions.

6. There have been sporadic reports advocating the use of non-ionic contrast media in the GIT.

C. Own Experimental Investigation

(see also chapters 5, 6, 7, 8 and 9)

Purpose

Perforation or leakage from the gastrointestinal tract can lead to the GIT contents entering the bronchi, lungs, mediastinum, pleural or peritoneal space. The contrast medium for evaluation of such leakages should therefore, ideally, produce no immediate or long-term toxic effects if leakage should occur in any or all of these places. The toxic effects of the routinely used contrast media for GIT evaluation ie. barium sulphate and gastrografin were partly known in certain anatomical locations (eg. lungs and peritoneum), but there is hardly any literature available on the effects of these CM in other anatomical areas ie. mediastinum and pleura.

It was also not known from the literature study as to what effects the bronchographic contrast media might have on the pleura, peritoneum and mediasinum (the effects in the lungs being known). The newer lower osmolality iodine containing water-soluble media Amipaque, Omnipaque and Hexabrix had not been used in the gastrointestinal tract for the evaluation of perforations at the start of the present experimental study. There was also very little known as to what effects these CM might have on the lungs, media-stinum, pleura and peritoneum. Moreover there is no literature available, which compares the reactions of all the possible contrast media, which could be used for evaluation of GIT leakage in all the major areas, where such leakage can occur.

Experimental Design and Method

— Type of animal used:
— Rats (Wistar Strain) outbred stock, wu/cpb (Zeist, The Netherlands), weighing ± 300 gms.
— Contrast media used were the following:
— Pure barium sulphate
— Micropaque
— Gastrografin
— Dionosil
— Hytrast
— Amipaque (Omnipaque in pleura)
— Hexabrix
— Control groups received:
— Physiological saline
— Anaesthetic only
— Contrast media effects studied on:
— bronchi and lungs
— mediastinum
— peritoneum
— pleura

One hundred and eighty rats were used for each of the experiments for evaluation of CM reactions on lungs, mediastinum and peritoneum. These were divided into nine groups of 20 rats, 7 groups receiving different CM as listed previously and two control groups. These groups of 20 rats were further divided into subgroups of 4 rats according to the day of sacrifice (day 1, 2, 4, 8 and 42) (see chapters 5, 6 and 7).

For the experiment on the CM reaction on pleura, one hundred and eight rats were divided into nine groups of 12 rats each, seven groups receiving different contrast media and two control groups. These were subdivided into three groups of 4 rats sacrificed at day 1, 8 and 42 (see chapter 8).

The toxicity of Hytrast in the peritoneum was evaluated on 20 rats divided into five groups of 4 rats each (four groups receiving Hytrast and one receiving physiological saline).

Anaesthesia. Hypnorm® (fluanisone and phentanyl citrate) was used for anaesthetising the rats in the experiments on lungs, mediastinum and peritoneum. Ether was used as the anaesthetic in the experiments on pleura and on the 'toxicity of Hytrast'. An overdose of the same anaesthetic was used to sacrifice the animals at specific intervals as stated previously. Surgical technique was kept as simple as possible and all animals were treated the same way in order to have a uniformity of the final result.

Radiographs were obtained immediately before and after the introduction of contrast medium and at regular intervals (day 2, 4 and weekly for the longer surviving groups) as well as on the day of sacrifice.

At autopsy, the gross appearances of the various regions and organs were noted according to a specific protocol set up for each of the experiments. The tissues for microscopic study were emersed in formalin solution and labelled. These were cut into thin (4μm) histological sections which were mounted and stained with Haematoxylin and Azophloxin. In a few instances additional elastica v Gieson staining was also used.

All the histological slides were studied blindly without prior knowledge of the contrast medium used.

The histological grading was based on the type and severity of the reaction. A plus or minus scoring system with 3 plus as the maximum reaction was used for grading the histological tissue reactions. For the statistical analysis the x^2 test for K independent samples was applied (for the determination of the level of significance) in most of the experiments.

Summary of results

It was clear from the experimental study that both pure and commercial (Micropaque) barium sulphate produced very severe histological reactions in all tissues examined. Hytrast

gave quite a severe histological reaction in lungs, pleura, and mediastinum and it was fatal in the peritoneum in the doses used for the experiment. The precise cause of death of the animals due to Hytrast in the peritoneum could not be defined on the basis of this experiment, therefore, a further experimental study was conducted to define the toxicity of Hytrast in the peritoneum (see chapter 9). Severe exudative, necrotizing peritonitis appeared to be the most likely cause of death due to Hytrast in the peritoneum. Dionosil gave rise to a significant reaction in the peritoneum and mediastinum, a not significant reaction in the lungs and an insignificant reaction in the pleura. Barium sulphate both pure or commercial, Hytrast and Dionosil are, therefore, not suitable for use in case of leakage from the GIT. The experimental study on the rat lungs demonstrated that Hexabrix and Amipaque gave the least tissue reaction.

The minimum reaction in the mediastinum of rats was seen in Amipaque, Hexabrix and Gastrografin groups.

The experiment on the rat peritoneum showed that Hexabrix gave the least reaction with Amipaque and Gastrografin not being significantly different from Hexabrix. In pleura Hexabrix, Gastrografin and Omnipaque gave the least reaction.

Conclusion based on the Experimental results

Pure barium sulphate Micropaque, Hytrast and Dionosil gave significant reaction in all or most of the tissues examined and are therefore unsuitable for use in suspected GIT perforation or leakage. Gastrografin caused significant reaction in the rat lung in the present experimental study and also in other experimental works published in the literature. A further detailed histological study was also undertaken to compare the effects of Hexabrix, Amipaque and Gastrografin, on the rat lung, which again demonstrated the significant reaction caused by Gastrografin compared to Amipaque and Hexabrix (see chapter 5b). The lower osmolality contrast media Amipaque, Omnipaque and Hexabrix appear to give very slight or no significant reaction when all the tissue reactions are considered together.

D. Own clinical experience

Upper gastrointestinal tract (see also chapter 10)

On the basis of some of the experimental results, clinical use of Hexabrix in the UGIT was started ± 4 years ago in cases where leakage outside the UGIT could be suspected. The majority of the patients examined with Hexabrix were postoperative. There is a higher risk of aspiration in the postoperative patients due to a high position of anastomosis (particularly when narrow), or due to an abnormality in the swallowing mechanism eg., after reconstructional surgery in the pharynx region. The postoperative patients often have to be examined in the supine position which further increases the chances of aspiration. Extra care is, therefore, required

in the choice of a correct CM for the radiological evaluation of such patients. The results of the first two year period have been evaluated and have shown no untoward effects due to the use of Hexabrix. It is clear that other lower osmolality contrast media such as nonionic Omnipaque may also be clinically safer, due to their lower osmolality, compared to Gastrografin.

Small bowel and colon

Small bowel examination may be required with a water-soluble contrast medium when there is a suspicion of leakage. It is advisable to use a low osmolality contrast medium such as Hexabrix or nonionic media, such as Omnipaque. These contrast media due to their lower osmolality do not get diluted and give better diagnostic results. Another reason for using low osmolality media is the possibility of regurgitation and aspiration which can be an added risk particularly in the postoperative patients. For the evaluation of large bowel with water-soluble contrast media in case of possible postoperative leakage or perforation, a conventional ionic contrast medium such as Gastrografin can be used as there is normally no risk of aspiration in such examinations. However, when large quantities of conventional hypertonic contrast media are used in small children and debilitated adults there is a high risk of causing dehydration and possible circulatory collapse. Moreover Gastrografin also appears to have an irritating effect on the bowel mucosa. It is, therefore, advisable to use a lower osmolality contrast medium in large bowel examinations particularly in small children and dehydrated adults to prevent untoward effects.

E. Method of radiological evaluation of leakage

— A relevant clinical history of the patient is essential before starting the examination. Upper GIT perforation can sometimes be insidious particularly when not accompanied by the typical clinical signs.

— In postoperative cases the exact nature of surgery should be known before starting the radiological evaluation.

— A plain radiograph of the chest may give diagnostic clues such as pneumoperitoneum, pneumomediastinum, subcutaneous air, pleural effusions or lung atelectases and therefore should always be taken before contrast examination.

— Oesophagogram using water-soluble contrast medium of low osmolality remains the most important tool for diagnosis of the exact site with extent of perforation. The contrast oesophagogram should include views in different positions, eg., supine or/and erect frontal, lateral and oblique etc., and in difficult cases lateral decubitus and horizontal ray views in supine and prone positions may be required.

— For perforations in the abdomen eg., from the intestines, same rule applies, appropriate history of the patient, a plain supine view of the abdomen along with an erect abdominal and chest view to see if free air is present. If the patient is unable to stand, a lateral decubitus or a horizontal-ray supine view should be taken to detect any free air in the peritoneal cavity. To detect small quantities of free air in the abdomen the patient should stand (or sit) or lie on the left side (lateral decubitus view) for at least 5-10 minutes before taking the X-ray. A contrast medium examination can then follow if required.

— The use of a rapid filming technique such as video-recording is very useful in difficult examinations particularly in patients with tendency to aspirate (such as postoperative patients).

— The amount of contrast medium used for examination should not be excessive and should be only as much as is necessary for the demonstration of the leakage or aspiration etc. For the oesophagus examination 20-50 ml of CM are usually enough, but up to 100 ml may be required.

F. Other indications for the use of lower osmolality water-soluble contrast media

— Obstruction due to foreign body in oesophagus to confirm diagnosis before endoscopy.

— Evaluation of severe strictures in oesophagus eg., after lye ingestion.

— To evaluate upper gastrointestinal tract obstruction prior to surgery in certain circumstances.

— Evaluation of congenital tracheo-oesophageal or broncho-oesophageal fistula.

— Evaluation of disordered swallowing.

— Peritoneography or herniography.

— In patients with possible acute diverticulitis in order to confirm clinical diagnosis and exclude other pathology.

— To evaluate cutaneous fistulae which may have a connection with the lung, pleural or peritoneal cavity or mediastinum.

— Certain pediatric examinations where use of barium sulphate may not be desirable eg. upper gastrointestinal obstructions with danger of vomiting and regurgitation.

— To evaluate unexplained pneumopertitoneum.

— For evaluation of non-functioning colon or rectum (when not is use for a long time) in patients with colostomy or ileostomy.

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Experimental evaluation of various available contrast agents for use in the upper gastrointestinal tract in case of suspected leakage

EFFECTS ON LUNGS

ABSTRACT

The reactions of seven contrast agents—pure barium sulphate, Micropaque, Gastrografin, Dionosil, Hytrast, Amipaque and Hexabrix—on the bronchi and lungs of rats were studied. This work was undertaken to find a safe gastro-intestinal contrast agent for use in post-operative patients where aspiration may be an accompanying risk. Amipaque and Hexabrix produced no significant histological reaction in the lungs and would, therefore, appear to be suitable for use in such cases.

The present experimental study was triggered by the unsatisfactory evaluation of and/or serious reactions occurring after the use of conventional gastro-intestinal contrast media in post-operative patients who have had some form of upper gastro-intestinal surgery. The choice of a suitable and safe contrast medium in such cases is sometimes difficult, because it may leak outside the lumen of the gut into the mediastinum, pleura or peritoneum or be aspirated into the lungs. The ideal contrast agent, therefore, should produce no immediate, delayed or long-range significant reactions in the mediastinum, pleura, peritoneum or lungs. It should, at the same time, have adequate radiographic qualities for evaluation of the region in question. The present article deals with the effects of various available gastro-intestinal and bronchographic contrast media and also two relatively new contrast agents, metrizamide (Amipaque) and ioxaglate (Hexabrix), on the bronchi and lungs of rats.

MATERIAL AND METHOD

180 male rats (Wistar strain, outbred stock, WU/Cpb) (Zeist, The Netherlands), weighing between 239 and 317 g, were used. The rats were divided into nine main groups of 20, seven receiving contrast agents (see below), and two control groups (one receiving saline solution and the other nothing).

1. Pure barium sulphate suspension, 90% weight/volume (w/v)
2. Commercial barium sulphate suspension, 100% w/v (Micropaque, Laboratories Nicholas Gaillard)
3. Sodium and meglumine diatrizoate 370 mg I/ml (Gastrografin, Schering, Berlin)
4. Aqueous suspension of n-propylester of 3 : 5-diiodo-4-oxopyridin-1-ylacetate (Dionosil, Glaxo Laboratories Ltd., Greenford, Middx.)
5. Aqueous suspension of propyl-2 : 3 diol 3 : 5-diiodo-4-pyridone (NPP) and 3 : 5-diiodo-4-pyridone (DIP) (Hytrast, Guerbet, Paris)
6. Metrizamide in a concentration of 370 mg I/ml (Amipaque, Nyegaard, Oslo)
7. Meglumine and sodium ioxaglate 320 mg I/ml. (Hexabrix, Guerbet, Paris)
8. Physiological saline (0.9% sodium chloride solution)
9. Anaesthetic only.

Each group was further divided into five sub-groups of four rats each, (sacrificed on different days). The animals were anaesthetised with an intramuscular injection of ± 0.25 ml, Hypnorm® (fluanisone and phentanyl citrate). They were then fixed on a rat board and through a small tracheostomy a thin polythene tube, 1.6 mm in diameter, attached to a syringe was introduced into the left main bronchus. Correct positioning of the catheter was usually quite easy with the help of fluoroscopy. 0.03 ml (equal to about 10 ml in a 70 kg man) of one of the contrast agents or physiological saline was introduced through the catheter into the left main bronchus. The catheter was then removed and the tracheostomy site at the neck closed with a surgical clip.

Radiographs of the lungs were taken immediately before and after the introduction of contrast agent and on the day of sacrifice. The long-surviving groups were, in addition, X-rayed weekly.

A sub-group of four animals from each main group was sacrificed by an overdose of sodium pentobarbitone, at 1 day, 2 days, 4 days, 8 days and 42 days after receiving the contrast medium. At dissection, the heart, lungs and trachea were removed from the thoracic cavity. The lungs were perfused with 10% buffered formalin solution (Farwell & Lewis, 1970) and then immersed in formalin for at least 10 days before histological sections of the left lungs were prepared and stained with haematoxylin and eosin.

Histological grading

Histological study was based on the type and severity of the inflammatory reaction in the lung
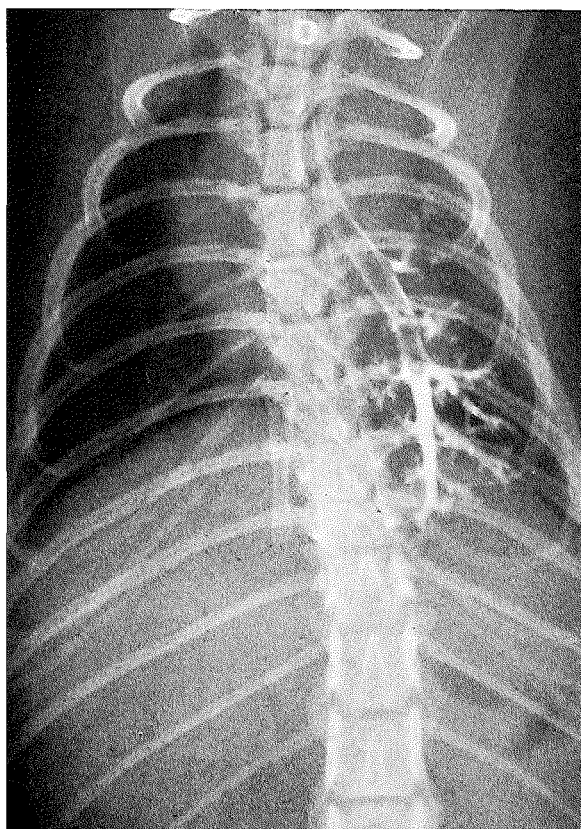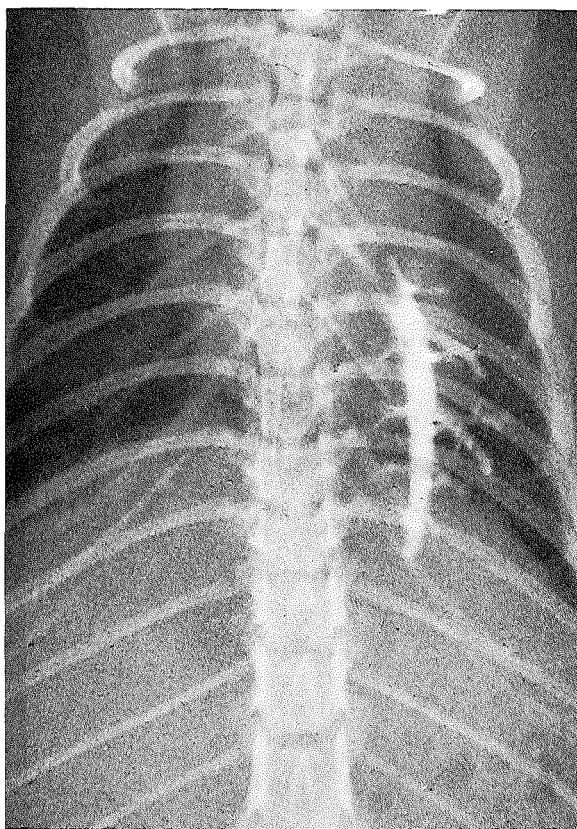
Fig. 1.

Left lung bronchograms with (A) Micropaque, (B) Dionosil.

parenchyma, presence or absence of bronchial changes and total area of involvement. The presence or absence of contrast agent was also noted. The following grading system was used for evaluation of the histological reactions.

Grade 0: normal or no significant reaction.
Grade +: mild reaction with 5–20% of lung area involved.
Grade + +: moderate reaction with 20–50% of lung area involved.
Grade + + +: severe reaction with > 50% of lung area involved. χ^2 test (for k independent samples) was applied for statistical analysis.

RESULTS

Most of the animals tolerated the anaesthetic and tracheostomy well, although approximately 5% died. (Repeats were done for those who died.) Deaths were fairly equally divided among the groups including the control.

Radiographic findings

The chest radiographs were useful, initially to confirm the presence of contrast medium and later to visualise any residual contrast medium or gross pulmonary abnormalities. Dionosil aqueous, Hytrast, Micropaque and pure barium sulphate all produced good quality bronchograms (Fig. 1). Micropaque and pure barium sulphate were visible on serial weekly radiographs as multiple small patchy densities until the 42nd day (Fig. 2), although fewer and somewhat less dense than in the beginning. Tiny residues of Hytrast were also visible radiographically until the eighth day. Other pulmonary abnormalities such as areas of collapse consolidations could not be clearly defined on the chest X ray.

Gastrografin, Amipaque and Hexabrix bronchograms were of comparatively poor quality and the contrast agent became faint within a few minutes after introduction into the left bronchus. No trace of these water-soluble contrast agents could be seen on the 24 h chest radiographs.
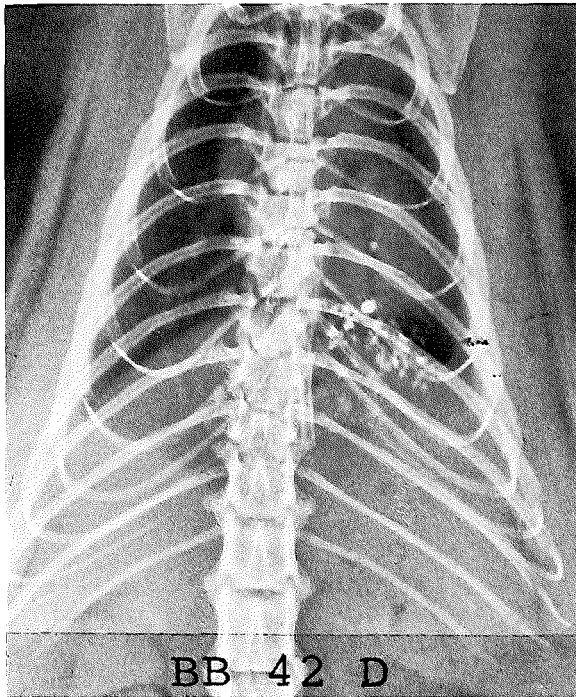
FIG. 2.

Chest radiograph taken at 42 days showing barium densities still present in the left lower lobe region.
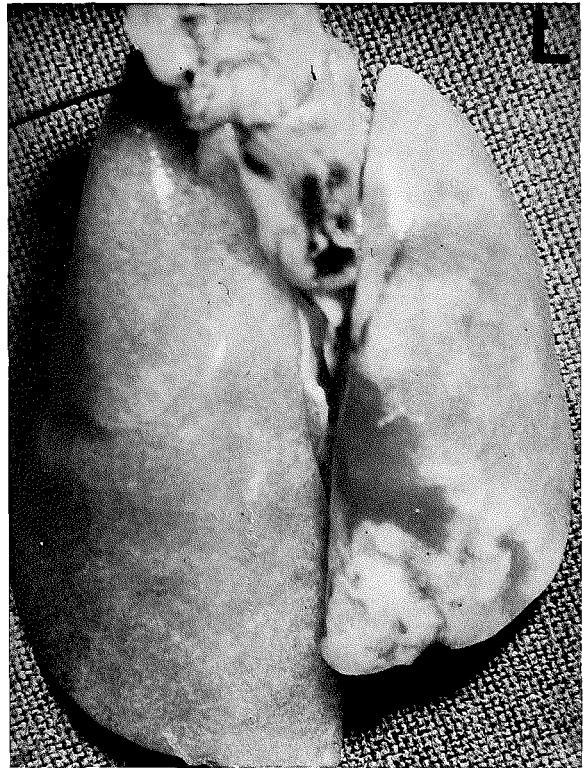

FIG. 4.

The left lung appears less distended after perfusion, with dark areas suggestive of consolidation.

FIG. 3.

Gross specimen of lungs showing no abnormality.

Pathological observations

Gross examination. At dissection the surface of the left lung either appeared absolutely normal (Fig. 3) or showed small or large dark red areas (Fig. 4), with almost complete lung involvement in some cases (Fig. 5). These dark red areas were macroscopically suggestive of collapse consolidation.

Histological appearances

Pure barium sulphate. At 24 and 48 h the larger bronchi were filled with contrast material (Fig. 6). Around the blood vessels some oedema was noted. Polymorphonuclear and mononuclear cell infiltrate around blood vessels and bronchi was seen. On the fourth day histiocytic reaction was present, and the contrast material seen in smaller bronchi and alveoli was mostly extracellular. On the eighth day small patchy areas of bronchopneumonia were noted. At this stage the contrast agent was found in macrophages, and epitheloid cell granulomata were formed in the lung parenchyma (Fig. 7). At 42 days granulomas were also noted intramurally in the walls of the bronchi.

Micropaque. On the first and second day the larger bronchi were seen to be filled with contrast agent: some was also seen in alveolar spaces. Polymorphonuclear
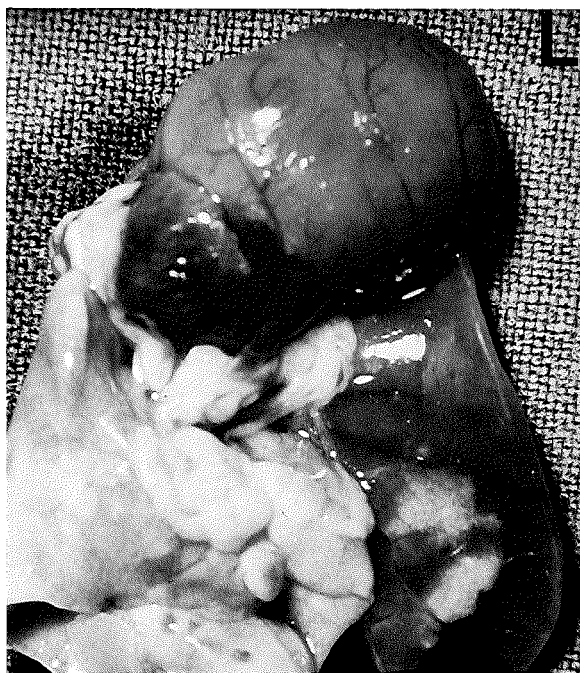
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FIG. 5.

The left lung shows complete consolidation on this gross specimen and appeared dark red in colour. The right lung appeared normal; heart is seen at the top of the picture.

FIG. 7.

Histological section showing circumscribed granuloma formation. The cytoplasm of the histiocytic cells is filled with barium sulphate giving them a granular appearance (H and E 380 ×).

cells were seen at this early stage in smaller bronchi and alveolar spaces. On the fourth day contrast agent was seen within the histiocytes in alveolar spaces. On the eighth day a granulomatous reaction with macrophages filled with contrast agent was noted. On the 42nd day focal granuloma-like reaction without giant cells was seen.

Hytrast. On the first and second day crystals of contrast agent were seen diffusely in some areas of lung parenchyma. Extensive polymorphonuclear reaction in the peribronchial alveolar spaces was noticed. On the fourth and eighth days contrast material was intracellular and the reaction was mainly histiocytic, with a few polymorphonuclear cells in alveolar spaces and small bronchi. On the 42nd day a few histiocytes and polymorphs were still seen within the alveolar spaces.

Gastrografin. On the first and second days a perivascular infiltrate with mononuclear cells was seen (Fig. 8). A little alveolar inflammatory infiltrate with histiocytes and collapse of the lung was also noted in certain areas. On the fourth day some swelling and desquamation of the alveolar epithelium was present. A focal histiocytic infiltrate around the blood vessels with a few mononuclear cells and lymphocytes was also
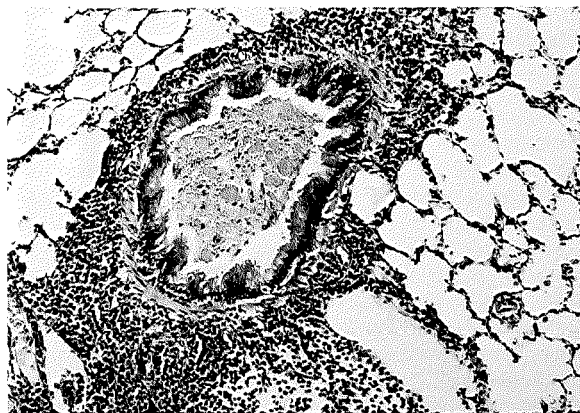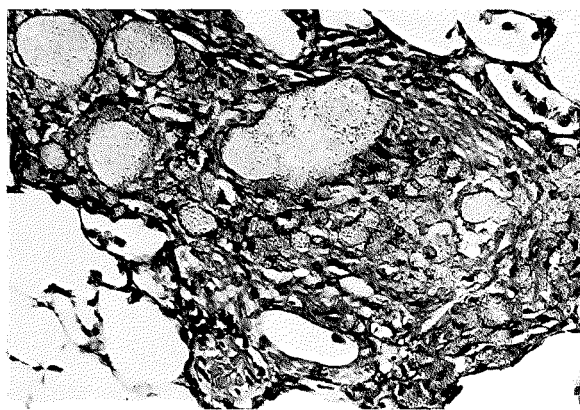

FIG. 6.

Histological section showing the lumen of the small bronchus filled with barium sulphate. An inflammatory infiltrate is seen around the bronchus. (Haematoxylin and eosin 150 ×).
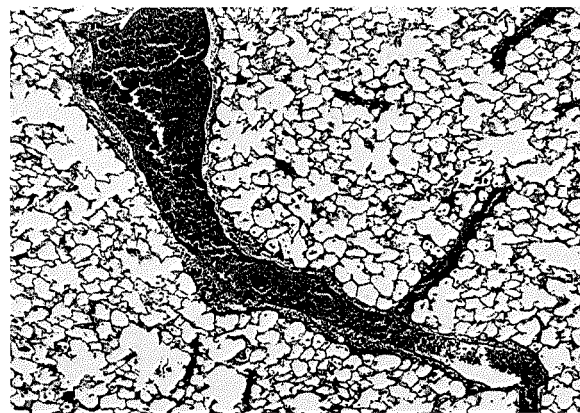

FIG. 8.

Histological section of lung two days after Gastrografin introduction, showing a blood vessel filled with blood and a rim of perivascular inflammatory infiltrate. (H and E 60 ×).

noted. On the eighth day there was a similar but less marked reaction. On the 42nd day there was slight perivascular infiltrate but otherwise no specific changes.

Dionosil. On the first day some proteinous material was noted in alveolar spaces. A slight macrophage reaction was also present. On the second, fourth, eighth and 42nd days slight perivascular infiltrate and alveolar epithelial swelling were noted.

Amipaque. On the first and second days a few tiny bronchopneumonic patches were noted. On the fourth day histiocytes, plasma cells, lymphocytes and a few polymorphonuclear cells were seen in the lumen of the bronchi. A slight peribronchial and perivascular infiltrate was present. On the eighth day mononuclear infiltrate was noticed around the blood vessels. No particular changes were seen on the 42nd day.

Hexabrix. On the first day no changes were seen. From the second to the eighth days there was a slight polymorphonuclear reaction in the perivascular regions with some oedema in places. No changes were seen on the 42nd day.

Physiological saline. On the first day some areas of collapse were seen. On the second day there was a little perivascular oedema and slight mononuclear infiltrate in the lung parenchyma. From the fourth to the 42nd day no significant reaction was noted.

Controls

On the first, second and fourth days no reaction was seen. On the eighth day some perivascular oedema and infiltration with mononuclear cells and a few histiocytes were noted. On the 42nd day a few focal areas of reaction with histiocytes in the perivascular spaces could be seen.

Table I summarises the results of the histological grading for all rats. The χ^2-test indicated a highly significant difference between groups receiving different treatments (right-hand column of Table I; $p < 0.001$). The saline and the control groups did not differ, and so they were combined to form one control group. Dionosil, Amipaque and Hexabrix did not induce significant reactions in the lung, as compared with the saline/control group. There was a significant difference in the reaction between pure barium sulphate, Micropaque, Hytrast and Gastrografin groups, ($p < 001$), as compared with the saline/control group. For these last four groups there exists also a significant difference in reaction in early and late phases with decrease in reaction by 42 days.

DISCUSSION

An attempt is made in this animal experimental study to find a safe and suitable contrast agent for the radiological demonstration of the upper gastro-intestinal tract in cases where leakage may be suspected, particularly post-operatively. Since the contrast agent used for examination of such patients can enter the trachea and lungs, mediastinum, pleura or peritoneum, we decided to evaluate the reactions in all these regions.

TABLE I

REACTION OF VARIOUS CONTRAST AGENTS ON THE BRONCHI AND LUNGS OF 180 RATS

Day of dissection	1	2	4	8	42	Total
Barium	+++	+++	++	+++	++	
sulphate	+++	++	++	+++	++	
(pure)	+++	++	++	+++	++	46*
	+++	++	0	+++	+	
Micropaque	+++	+++	+++	++	++	
	+++	++	++	++	++	
	++	++	++	++	++	41*
	++	+	+	+	++	
Hytrast	++	++	++	++	++	
	++	++	+	++	+	
	++	++	+	++	0	30*
	+	++	+	+	0	
Gastrografin	++	++	++	++	++	
	++	0	++	++	+	
	++	0	+	++	0	23*
	+	0	0	0	0	
Dionosil	+++	+	+	++	+	
	++	+	+	0	+	
	+	0	+	0	0	16
	+	0	0	0	0	
Amipaque	+	+	++	0	0	
	+	0	+	0	0	
	+	0	0	0	0	7
	0	0	0	0	0	
Hexabrix	0	++	0	+	0	
	0	++	0	0	0	
	0	0	0	0	0	5
	0	0	0	0	0	
Physiological	++	+	0	0	0	
saline	++	+	0	0	0	
	+	+	0	0	0	8
	0	0	0	0	0	
Control	+	0	0	++	0	
	0	0	0	0	0	
	0	0	0	0	0	3
	0	0	0	0	0	
Total	52	37	30	37	23	

*$p < 0.001$ Compared to physiological saline/control group
0   no significant reaction
+   mild reaction
+ +   moderate reaction
+ + + severe reaction

We started by studying the reaction of various contrast agents on bronchi and lungs and the present article describes these results. This was considered of primary importance as the inhalation of certain water-soluble contrast agents may prove immediately fatal (Ansell, 1968). We have used both the bronchographic and conventional gastrointestinal contrast agents as well as the water-soluble non-ionic contrast Amipaque and recently synthesised Hexabrix.

Our study appears to show no significant statistical difference between the reaction produced by pure barium sulphate (without any coating agents or other

additives) and commercial barium sulphate (Micropaque) as far as the effects in the lungs are concerned (Table I). Arrigoni (1933) injected pure barium sulphate intratracheally in rabbits and rats. He reported histological findings of foreign body reaction including fibrosis and tubercle formation. Huston et al (1952) studied the effects of endotracheal injection of barium suspensions in rats and observed very little cellular reaction and no fibrosis. In our study the reaction to barium sulphate in the lungs was very similar to that shown in the study by Willson et al (1959) who thought that a considerable amount of histological changes were due to the mechanical plugging of the bronchi by barium sulphate. The degree of collapse of the lung and inflammatory reaction associated with such plugging of the bronchi was shown in our series by the extensive histological reactions seen in both pure barium and Micropaque. McAlister et al (1981) also reported profound alteration in blood gases, segmental atelectases, focal pneumonitis and fibrosis after direct introduction of barium sulphate into the lungs of experimental animals. At least two deaths have been recorded as a result of barium in the lungs of babies (Sauvgrain, 1969; Meradji, 1980). It appears, therefore, from the study of the literature as well as the present experimental work that barium sulphate, whether pure or in commercial preparations, would be harmful to the lungs and may even prove to be fatal, particularly in large quantities. Death and enhanced morbidity from this cause may occur more commonly than is reported (Ratcliffe, 1983).

Hytrast appeared to give a highly significant reaction compared with physiological saline. This crystalline contrast agent stayed visible histologically even at 42 days.

Gastrografin has produced a statistically significant reaction in our series. Ansell (1968) reported death from aspiration of one mouthful of Gastrografin in an adult with cor pulmonale. Aspiration of Hypaque (sodium diatrizoate) caused acute pulmonary oedema in a patient with Boerhaave's syndrome who died shortly thereafter (Chiu & Gambach, 1974). Reich (1969) described pulmonary oedema and death in anaesthetised rats following 0.5 ml/kg intratracheal Gastrografin. Frech et al (1970) also found pulmonary oedema and acute distress, following injection of 40% diatrizoate (Hypaque), which appeared to clear within several hours. Gastrografin is a water-soluble contrast agent identical with Urografin 76% (meglumine and sodium diatrizoate) except for addition of a flavouring agent (anise) and a wetting agent (Tween 80). It is highly hypertonic, with an osmolality of 1900 milliosmols, which is approximately six times that of plasma. This high osmolar activity results in an osmotic gradient which extracts a given quantity of fluid from the vascular compartment into the lung parenchyma and perivascular space, depending upon the amount of Gastrografin used and the length of contact with the bronchial and alveolar walls. This might be the reason for its irritating effect on the lungs and production of severe pulmonary oedema in certain cases (Margulis & Burhenne, 1973). In our series a very small quantity of Gastrografin in one lung was used, which appeared to dilute rapidly.

Dionosil appeared to cause a statistically insignificant reaction in the lungs; it is the contrast agent widely used for bronchography at present.

Amipaque caused no significant reaction in the lungs when compared with the control groups. Amipaque (metrizamide) is a water-soluble contrast medium which is non-ionic in solution and has consequently half the osmolality of monomer ionic agents with identical iodine concentration. Its measured osmolality is actually even less. A concentration of 170 mg I/ml is isotonic with blood, and a concentration equal to that of Gastrografin, i.e., 370 mg I/ml, has approximately double the osmolality of plasma.

Hexabrix caused minimum histological reaction—no different from physiological saline. Hexabrix is a 2 : 1 mixture of meglumine and sodium salts of a newly synthesised ioxaglic acid, which is a mono-acid dimer and consists of two benzene rings to which are attached six atoms of iodine. One molecule of the salt in solution dissociates into one cation (sodium or meglumine) and one anion (ioxaglate radicle, containing six atoms of iodine) (Grainger, 1981). At a concentration of 320 mg I/ml Hexabrix has an osmolality of 580 milliosmol/kg water, which is about twice that of plasma.

The low-osmolality water-soluble contrast media Amipaque and Hexabrix have, so far, not been widely used for gastrointestinal purposes in adults. The use of Hexabrix in the paediatric gastrointestinal tract has been recently reported (Ratcliffe, 1983). This experimental study demonstrates low toxicity of Amipaque and Hexabrix when used in small quantities in the bronchi and lungs in rats which suggests they are safe for use in all circumstances where aspiration is a danger. They could be particularly useful in postoperative evaluation of patients with upper gastrointestinal surgery, where leakage and/or aspiration may be expected.

Other possible uses could be in patients with surgery of the larynx, evaluation of tracheo-oesophageal or broncho-oesophageal fistulae, lung fistulae and cavities and possibly for bronchography (for example, in children).

CONCLUSION

Barium sulphate and Micropaque produced extensive reaction in the rat lungs. Hytrast also produced significant reaction and would therefore be unsuitable. Gastrografin produced significant reaction in our series, may prove to be hazardous in cases of possible aspiration (Margulis, 1973; Ansell, 1968) and therefore should be avoided in such cases. Dionosil gave insignificant changes and is the contrast medium already widely used for bronchography. It may possibly be useful in the GI tract in specific situations. Our

experiment has shown Hexabrix and Amipaque to be almost as safe as physiological saline in bronchi and lungs and the histological reaction produced by these water soluble agents has been minimal. Hexabrix has the added advantage of being cheaper and available in ready-to-use solution. On the basis of these results we have already begun clinical use of Hexabrix for evaluation of the oesophagus in patients where a strong possibility of leakage and/or aspiration exists. We have so far come across no adverse reactions. (The results of this study will be published separately).

Experimental work on the reaction of contrast agents in the mediastinum and peritoneum is now completed and is being prepared for publication.

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Experimental evaluation of Hexabrix, Amipaque and Gastrografin in the lung

A DETAILED HISTOLOGICAL ANALYSIS

ABSTRACT
A detailed histological study of the effects of three iodine containing water soluble contrast media was carried out on the rat lung.
The results show that Amipaque and Hexabrix are safer than Gastrografin in the lung.

INTRODUCTION

Leakage from the gastrointestinal tract (GIT) can take place into the mediastinum, pleura, peritoneum or bronchi and lungs. The contrast medium used for the evaluation of the GIT leakage should therefore be safe in all these regions. Aspiration or leakage by means of direct fistula formation to the lung is of considerable importance as some contrast media eg., gastrografin in the lung can produce severe or fatal reaction (Ansell, 1968; Chiu & Gambach, 1974), most probably due to its high osmolality. In view of this detailed analysis of the histological reaction caused by Gastrografin and two lower osmolality contrast media Hexabrix and Amipaque, was carried out on the rat lung. The histological sections used were central coronal sections from the previous study (Ginai et al., 1984) and also additional sections taken from the periphery of the lung. The physiological saline and 'anaesthetic only' control groups were also included in the evaluation.
The purpose of this detailed histological study was to define:
1. If the histological reaction seen in the central coronal sections differed from that in the more peripheral sections of the rat lung.
2. The total histological reaction caused by different contrast media in the rat lung. Particular attention was given to the severity of the histological reaction which was defined by the type of cellular infiltration and extent of the lung area involved.

MATERIALS AND METHODS

The histological sections were taken from 5 main groups of 20 rats receiving one of the contrast media or control groups as mentioned below. The animals had been sacrificed at 1, 2, 4, 8, and 42 days after contrast medium introduction into the left bronchus and lung.
A total of 160 histological sections of rat lung stained with haematoxylin and azophloxin (with additional elastine and reticular staining in certain cases) were evaluated in the present study as follows.

(Hexabrix)	— Meglumine and sodium ioxaglate 320 mgm I/ml (40 sections: 20 central + 20 peripheral).
(Amipaque)	— Metrizamide in a concentration of 370 mgm I/ml (40 sections: 20 central + 20 peripheral).
(Gastrografin)	— Sodium and meglumine diatrizoate 370 mgm I/ml (40 sections: 20 central + 20 peripheral).
Physiological saline	— 0.9% sodium chloride solution (20 sections, only central coronal sections)
Control	— Anaesthetic only (20 sections, only central coronal sections)

The histological sections were scored on the basis of number and size of the inflammatory infiltrations and number and type of cells (mainly histiocytes, lymphocytes, polymorphs).
The central and peripheral sections were scored separately.

The histological grading was based on a plus or minus scoring system:
+ + + : severe reaction
+ + : moderate reaction
+ : mild reaction
± : minimum reaction

All the plus ratings were added up for the 4 animals in each subgroup. A mean of the peripheral and central sections (which were separately scored) was calculated to give the final reading for each subgroup.

RESULTS

Fig. 1 shows the results of the histological scoring.
The central and peripheral sections in general showed slight or no significant differences. The Gastrografin reaction was most severe on day 1 and 4, somewhat less on day 8 and had decreased considerably by the 42nd day.

Hexabrix showed almost no reaction on day 1, moderate reaction on day 2, which decreased on the 8th day and almost no reaction was seen by the 42nd day. A macrophage and lymphocytic reaction was mostly seen in case of Gastrografin but in case of Hexabrix there was a macrophage, lymphocytic and polymorphonuclear reaction. Amipaque gave very similar reaction to Hexabrix. Physiological saline and control groups also showed some inflammatory reaction consisting mainly of lymphocytes and polymorphonuclear cells.

This histological study using three water-soluble iodine containing contrast media brings several important points to light. It can be said that the central coronal left lung sections used in the previous experimental study on the rat lungs (Ginai et al., 1984) are not significantly different as far as the histological reaction is concerned from the additional peripheral sections of the same lungs, also evaluated in the present study.

The general histological reaction was somewhat more pronounced in the central sections compared to the peripheral, thereby suggesting that the central sections alone were adequate for the previous study (Ginai et al., 1984). In case of Gastrografin the initial reaction ie. on the 1st day was very severe and decreased slightly by the 8th day after which it was insignificant. In case of Hexabrix the initial reaction was insignificant and moderate to slight reaction was noted from the 2nd to the 8th day. Similar reaction is seen in case of Amipaque and also Physiological Saline and some reaction is seen even in the control (anaesthetic only) group.

This study confirms the findings of the previous experimental work on the contrast reaction in the rat lung (Ginai et al., 1984).

In conclusion it can be said that Gastrografin gives a significant reaction in the rat lung compared to Hexabrix, Amipaque, Physiological Saline and control groups and that Hexabrix and Amipaque do not differ significantly (See Fig. 1). The use of Gastrografin should, therefore, be avoided in any situations where leakage or aspiration to lungs is a possibility.

Since the completion of the experimental work on rat lung further experimental work on the rat mediastinum, peritoneum and pleura has been completed (Ginai et al., 1985, Ginai, 1985, Ginai, 1986).

The clinical use of Hexabrix was started $\pm$ 4 years ago in patients in whom the possibility of perforation from the upper gastrointestinal tract can be suspected particularly where leakage to lungs or aspiration is an accompanying risk. The use of Hexabrix in the first two year period has been evaluated and shows no side effects attributable to the contrast medium (Ginai, 1986).
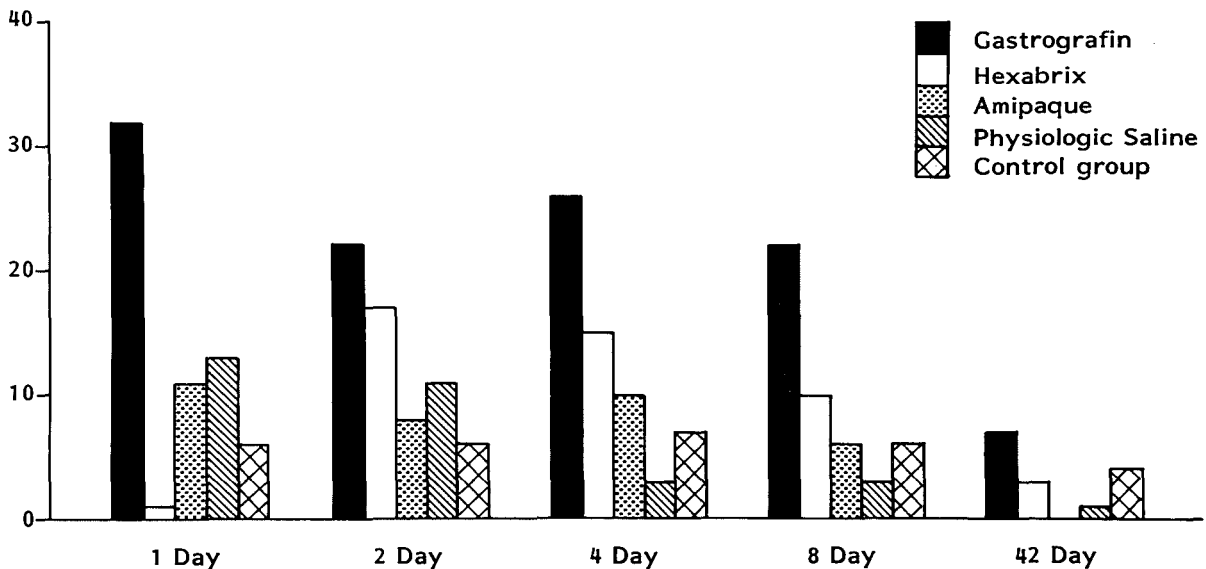

FIG. 1.
A histogram presenting the histological reaction caused by
Gastrografin, Amipaque and Hexabrix on the rat lung compared
with Physiological Saline and "anaesthetic only" control groups.

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Experimental evaluation of various available contrast agents for use in the upper gastrointestinal tract in case of suspected leakage

EFFECTS ON MEDIASTINUM

ABSTRACT

The tissue reaction of seven contrast agents—pure barium sulphate, Micropaque, Hytrast, Dionosil, Gastrografin, Amipaque and Hexabrix–was evaluated on the mediastinum of rats. This work was undertaken to define the most suitable and safe contrast agent for use in the upper gastrointestinal tract in cases where leakage outside the gut into the mediastinum, pleura or peritoneal cavity may be suspected and aspiration may be an accompanying risk. Keeping in mind the danger of aspiration, Hexabrix and Amipaque appear to be the safest contrast media for the mediastinum.

The present experimental work was carried out to find a safe and suitable contrast agent for use in the upper gastrointestinal tract (UGIT) in cases where leakage outside the lumen of the gut may be suspected, particularly postoperatively. The contrast agent used for radiological evaluation in such cases may leak outside the lumen of the UGIT, into the mediastinum, pleura or peritoneal cavity and/or be aspirated into the lungs. The effect of the contrast agents on lungs and bronchi has been investigated previously (Ginai et al, 1984).

The effects on the mediastinum of rats of the various conventional gastrointestinal and bronchographic contrast agents as well as of the non-ionic contrast medium, metrizamide (Amipaque) and the more recently synthesised ioxaglate (Hexabrix) are presented.

MATERIALS AND METHOD

180 male rats (Wistar strain, outbred stock, WU/Cpb) (Zeist, The Netherlands), weighing 245–343 g were used. They were divided into nine main groups of 20 rats; seven groups received contrast agents (see below) and two were control groups, one receiving normal saline and the other nothing.

1. Pure barium sulphate suspension, 90% w/v
2. Commercial barium sulphate suspension 100% w/v (Micropaque; Laboratories Nicholas Gaillard)
3. Sodium and meglumine diatrizoate 370 mg I/ml (Gastrografin; Schering, Berlin)

4. Aqueous suspension of n-propylester of 3 : 5-diiodo-4-oxopyridin-1-ylacetate (Dionosil; Glaxo, Greenford, Middx.)
5. Aqueous suspension of propyl-2 : 3 diol 3 : 5-diiodo-4-pyridone (NPP) and 3 : 5-diido-4-pyridone (DIP) (Hytrast; Guerbet, Paris)
6. Metrizamide in a concentration of 370 mg I/ml (Amipaque; Nyegaard, Oslo)
7. Meglumine and sodium ioxaglate 320 mg I/ml (Hexabrix; Guerbet, Paris)
8. Physiological saline (0.9% sodium chloride solution)
9. Anaesthetic only

Each main group was further divided according to the day of sacrifice, into five subgroups of four rats each. The rats were anaesthetised with ± 0.15 ml Hypnorm® (fluanisone and phentanyl citrate) and fixed to a ratboard. Through a low mid-line neck incision the trachea was exposed and 0.05 ml (equal to 14.0 ml in a 70-kg man) of one of the contrast agents or physiological saline was injected behind the trachea and oesophagus using a blunt needle. The contrast medium was injected as low as possible in the mediastinum under fluoroscopic control. The neck incision was closed afterwards with a surgical clip. The control group received only anaesthetic.

Radiographs of the thorax were taken in frontal and lateral projections after the injection of contrast medium and on the day of sacrifice. The long-surviving groups were also radiographed weekly.

Subgroups of four animals from each main group were sacrificed (using an overdose of sodium pentobarbitone) at 1 day, 2 days, 4 days, 8 days and 42 days after receiving the contrast medium. At dissection the region of the mediastinum, containing the trachea, oesophagus, large blood vessels and heart along with the spine, was removed and immersed in formalin for about three weeks. The vertebral column was then carefully removed and thick transverse sections of the rest of the mediastinum were made at arbitrary levels. These were then embedded in paraffin, cut in 4 μm
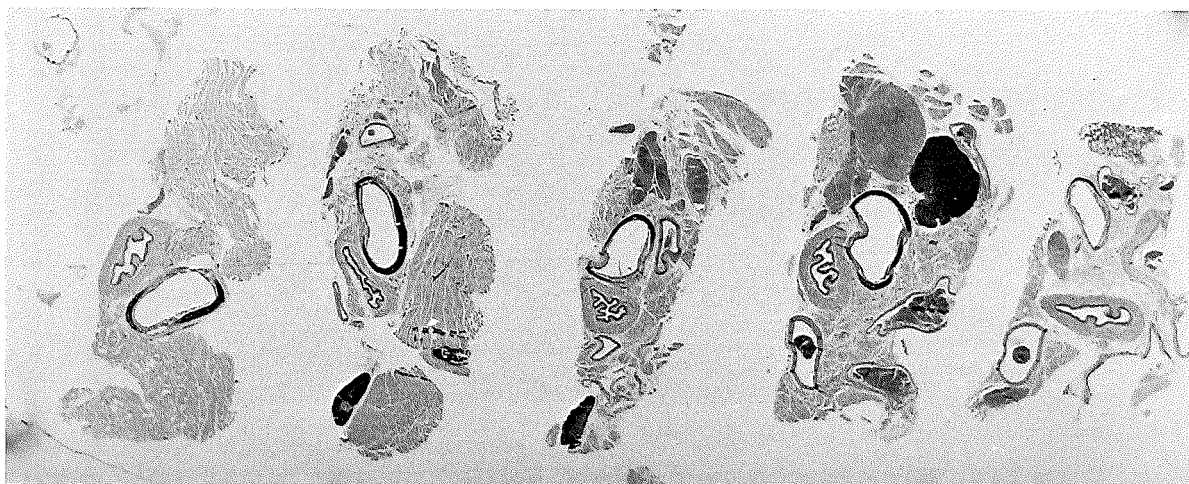
FIG. 1.

Transverse sections of the rat mediastinum at different levels stained with haematoxylin and azophloxin (H&A).

sections and stained with haematoxylin and azophloxin (Fig. 1).

Histological study was based on the type and severity of inflammatory reaction. The presence or absence of contrast medium in the mediastinum was also noted.

The histological reactions were graded according to the extent of the inflammatory reaction, as follows:

    0   = normal or no significant reaction
    +   = mild reaction
    + +   = moderate reaction
    + + + = severe reaction

The χ^2 test (for k independent samples) was applied for the determination of the level of significance.

RESULTS

The rats in general tolerated the surgical procedure and injection of contrast medium well. The anaesthetic was also fairly well tolerated. The general condition of the animals stayed good until the end. The 42-day group had put on considerable weight, as noted just before sacrifice. Eighteen of the 180 rats died: the deaths were fairly equally divided among various groups and subgroups, except that the Hytrast group had no deaths; but this was not significant (see Table I). Some deaths occurred shortly after the rats were anaesthetised before being X-rayed. Some deaths occurred during the night and the animals were found dead in the cage in the morning. Dissections were carried out whenever possible. The histological reaction in the 14 animals autopsied was not found to be unusual for the contrast medium used. In the remaining four rats who died the condition of the mediastinum could not be evaluated.

Radiological findings

On the frontal and lateral chest radiographs made immediately after the introduction of contrast medium,

barium sulphate, Micropaque, Hytrast, Dionosil, Gastrografin, Amipaque and Hexabrix were all clearly visible as well-defined collections (Fig. 2).

The contrast medium was mostly in a para-oesophageal and paratracheal situation in the lower cervical and upper mediastinal regions. In 14 animals it was located mainly anteriorly around the thymus. Contrast medium was noted in the pericardium in three rats and in the pleura in six rats, suggesting inadvertent surgical puncture at the time of injection. In one rat some contrast medium was found to be paraspinal as well as within the pleura and pericardium. Two rats showed pneumothorax and pneumomediastinum.

Barium sulphate and Micropaque stayed visible and practically unchanged in appearance on serial radiographs taken at weekly intervals until the 42nd day (Fig. 3).

Hytrast was also visible on radiographs till the 42nd day but reduced in quality and density.

Dionosil was faintly visible till the fourth day in some rats. Gastrografin, Amipaque and Hexabrix were not visible on the 24-hour radiographs of the chest.

Pathological observations

Gross examination of the neck, mediastinum and thorax was carried out by dissection to identify the presence or absence of contrast agent or other gross abnormalities suggestive of an inflammatory process. The sites of contrast agent or other abnormalities were noted as follows:—soft tissue of the neck, chest wall, paratracheal, paraoesophageal, perivascular, para-spinal, pleura, pericardium, lungs and diaphragm.

Pure barium sulphate, Micropaque and Hytrast were visible in moderate or fairly large quantities as chalky white material either around the oesophagus and trachea and extending down to the middle third of the mediastinum or lying anteriorly around the thymus. In

TABLE I

REACTION OF VARIOUS CONTRAST AGENTS IN THE MEDIASTINUM OF 180 RATS

Day of dissection	1	2	4	8	42	Total
Barium sulphate (pure)	+ +	+ +	+ +	+ +	+	
	+ +	+ +	+ +	+ +	+	
	+ +	* +	+ +	+ +	+	33
	+ +	*0	+ +	+ +	+	
Micropaque	+ + +	+ +	+ +	+ +	** —	
	+ + +	+ +	+ +	+ +	+	
	+ +	+	+ +	+ +	+	30
	0	* +	*0	+ +	0	
Hytrast	+ + +	+ + +	+ + +	+ +	+ +	
	+ + +	+ + +	+ + +	+ +	+	
	+ +	+ + +	+ + +	+ +	+	47
	+ +	+ + +	+ + +	+ +	+	
Gastrografin	0	+	+	+	0	
	0	0	+	* +	* +	7
	0	0	+	0	0	
	0	0	0	0	0	
Dionosil	+ +	+ +	+ +	+	0	
	+ +	+ +	+ +	+	0	
	+ +	+	* + +	+	0	20
	0	0	*0	*0	0	
Amipaque	+	+	0	0	0	
	0	0	0	0	0	2
	0	0	0	0	0	
	0	0	0	0	** —	
Hexabrix	+ +	+	+ +	0	*0	
	+	0	+	0	*0	
	0	0	0	*0	0	7
	0	0	0	** —	0	
Physiological saline	0	+	+	0	0	
	0	+	0	0	0	
	0	0	0	0	0	3
	0	0	0	** —	0	
Control	0	0	0	0	0	
	0	0	0	0	*0	
	0	0	0	*0	0	0
	0	0	0	0	0	
	35	33	39	29	12	

* = Animals who died but autopsy carried out
** = Animals who died but autopsy not carried out

0   = no significant reaction   + +   = moderate reaction
+   = mild reaction   + + + = severe reaction

these groups, perivascular contrast medium was noted in 10 rats; paravertebral in three. The inner chest wall looked dark red in some of those animals who had been dead for more than a few hours and these also showed dark red areas in the lungs. Contrast medium was seen around the pericardium in two rats and an abscess was noted in two rats at the site of the incision in the neck.

One rat (Micropaque, 8 days) showed much contrast medium spread throughout the thoracic cavity over pleura, pericardium, diaphragm, paraoesophageal, paratracheal and paravertebral regions; some pleural adhesions were also noted.

Histological appearances
*Pure barium sulphate.* Localised deposition of barium

sulphate was visible between trachea and oesophagus (Fig. 4) and in some cases around the thymus. Initially, the contrast agent was all extracellular and a histiocytic reaction was noted. From the 4th till the 42nd day increasing quantities of barium were noted to be intracellular and granuloma formation with histiocytic giant cells was seen at 8 days and 42 days. The contrast agent was mostly circumscribed at this stage (Fig. 5).

Micropaque. The reaction and contrast deposition in the mediastinum were very similar to those seen in the barium sulphate series except that giant cells were not seen even at 42 days.
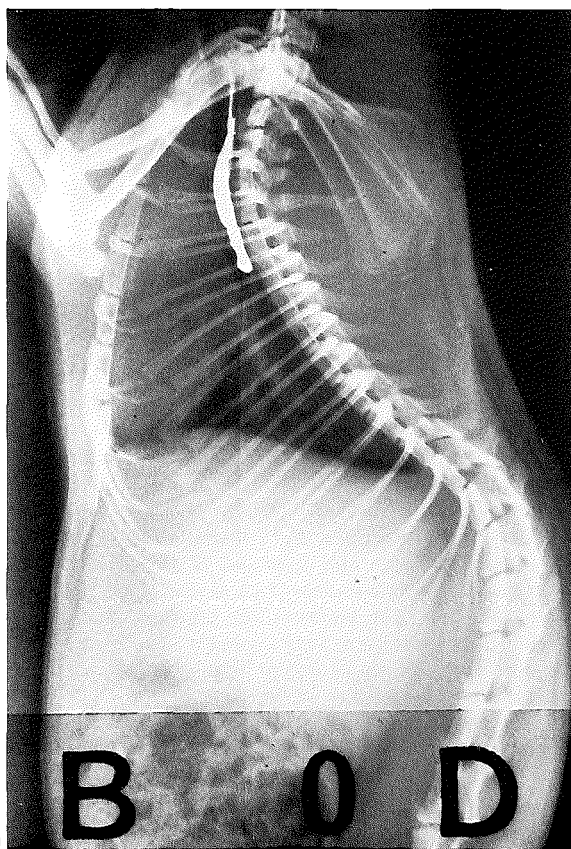
Hytrast. Crystalline contrast medium was noted with accumulation of polymorphs and nuclear dust amongst the contrast medium (Fig. 6). On the second day,
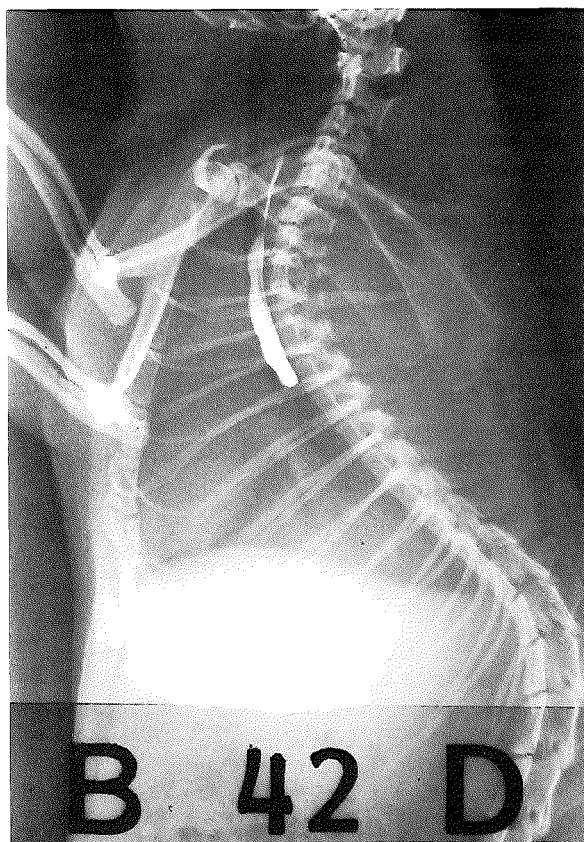
47

(A)

(B)

(C)
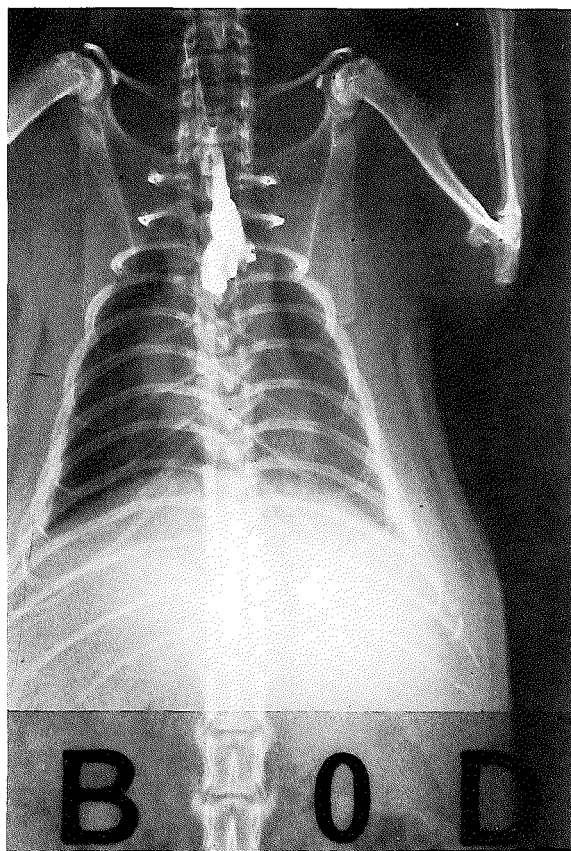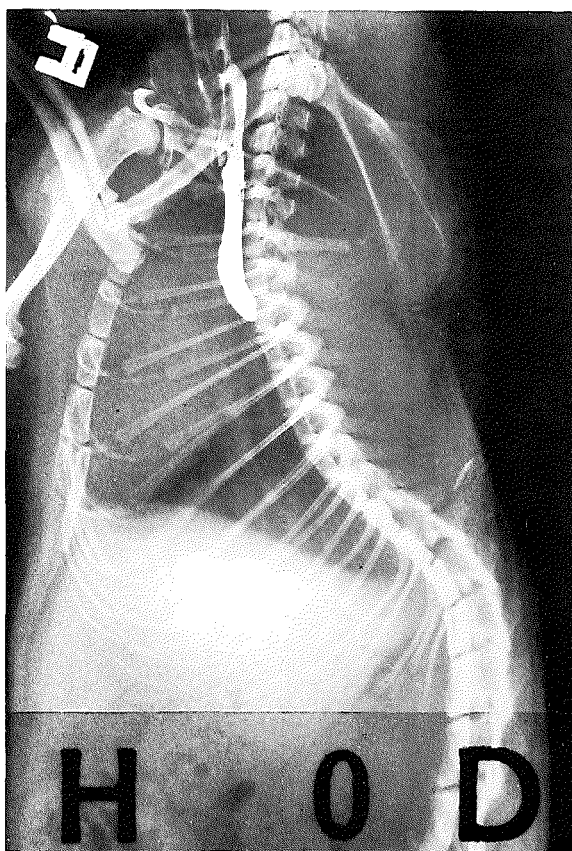
(D)

FIG. 3.

Same rat as in Fig. 2 (A, B) at 42 days after barium sulphate injection in the mediastinum showing no significant change in appearance.
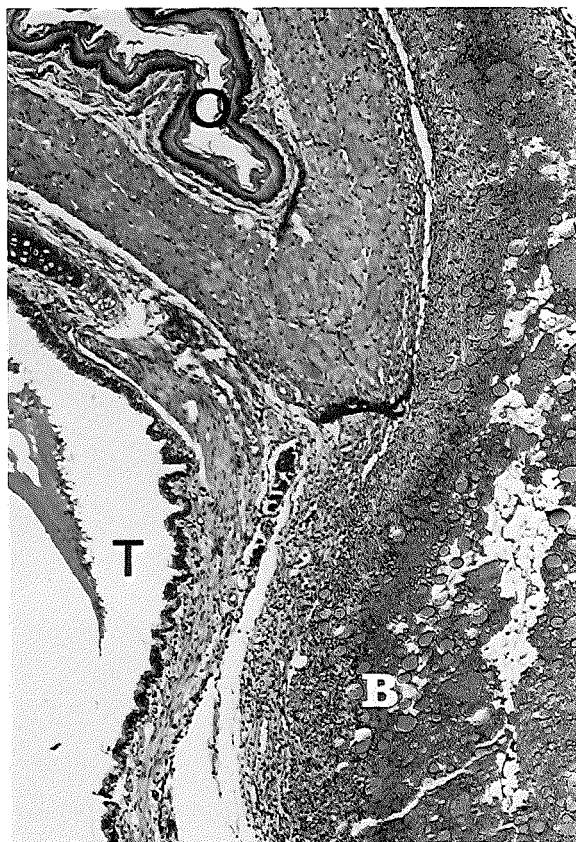

FIG. 4.

Histological section showing an initial collection of barium sulphate (B) adjacent to the trachea (T) and oesophagus (O). (H&A 60 ×).

fibrinous exudate was seen around the contrast deposition and on the 4th and 8th day fibroblasts and proliferating vessels were also noted. Granuloma formation was present at 42 days, showing histiocytes filled with contrast medium and giant cells (Fig. 7).

Dionosil. Fibrohistiocytic reaction was seen in the early stages. The cytoplasm of some of the fibrohistiocytic cells contained basophilic staining material (probably contrast residue). In the later stages at 4, 8 and 42 days, practically no tissue reaction was noted except for a few giant cells.

Gastrografin. No contrast was visible. Some oedema and polymorphonuclear leucocytes were noted in the paratracheal region on the first day and a fibroblastic

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FIG. 2.

PA (A) and lateral (B) radiographs of the chest showing barium sulphate in the mediastinum immediately after contrast injection. Lateral view with Hytrast (C) and Hexabrix (D) in the mediastinum.
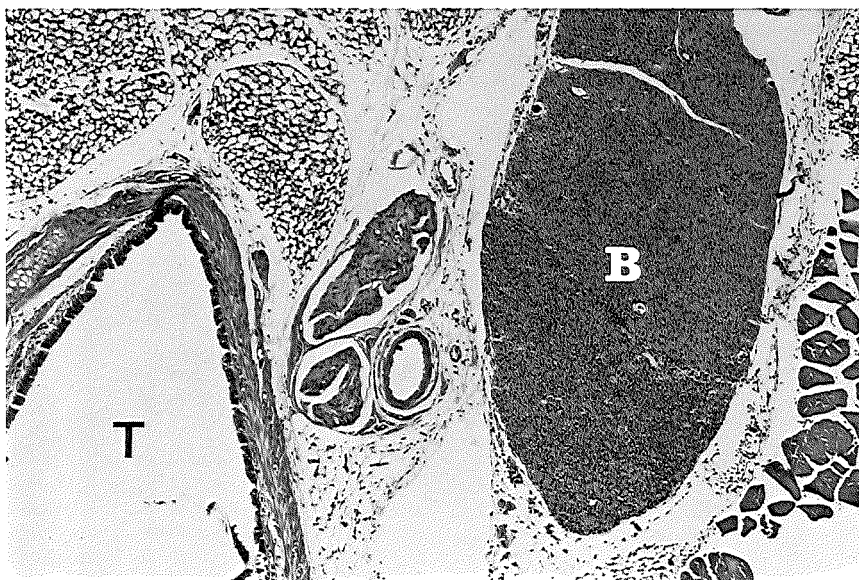
reaction was seen on the second and fourth days. No specific reaction was present at the 8 and 42 day stages.

Amipaque, Hexabrix, physiological saline and control groups. The rats in these groups showed minimal nonspecific reaction or no reaction at all.

Table I summarises the results of the histological grading for all rats. The χ^2 test indicated a highly significant difference between groups receiving different contrast agents ($p < 0.001$). Hytrast, pure barium sulphate, Micropaque and Dionosil produced highly significant reactions ($p < 0.001$) compared to saline/control group (saline and control groups were joined together to form one group as these two were not significantly different). Gastrografin and Hexabrix produced a slight reaction compared to control groups ($p = 0.05$). Amipaque produced no significant reaction in the mediastinum compared to saline/control group. The χ^2 test indicated a highly significant difference between the reactions observed on the different days of sacrifice ($p < 0.001$). In general, most reaction was seen in the first four days with decrease by the 8th day and further decrease by 42 days.
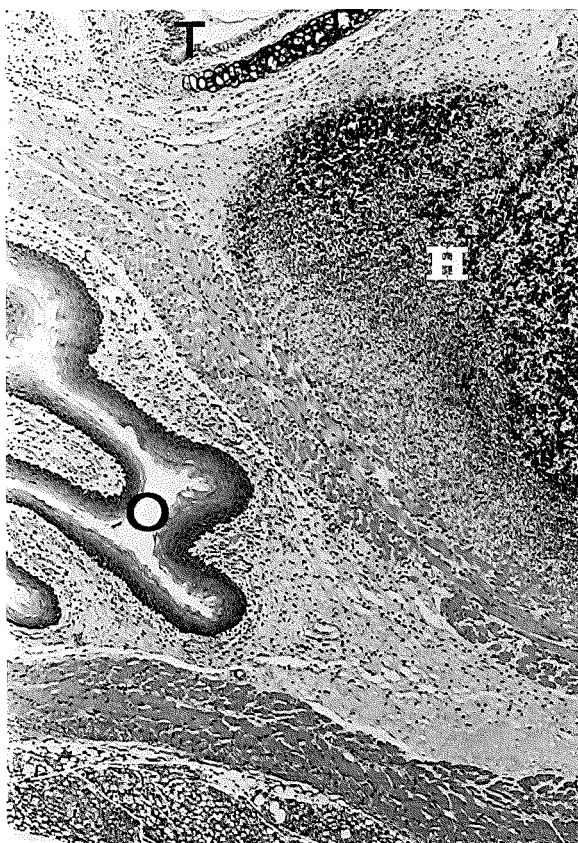
FIG. 6.

Histological section two days after injection of Hytrast (H) shows an ill defined collection of dark staining Hytrast cystals between the trachea (T) and oesophagus (O). (H&A 60 ×).

DISCUSSION

The present animal experimental work was undertaken to evaluate the various available gastrointestinal and bronchographic contrast media and two relatively recent water-soluble contrast agents, Amipaque and Hexabrix, in cases where leakage outside the lumen of the gut may be suspected, particularly in postoperative assessment of anastomoses. In such examinations there is a possibility of leakage of contrast agent into the mediastinum, pleura or peritoneum or aspiration into the lungs. This last is of primary importance, as deaths have been known to occur following aspiration of certain water-soluble contrast agents used for demonstration of the upper gastrointestinal tract (Ansell, 1968; Chiu & Gambach, 1974). Our initial experimental work was concerned with the reactions of various contrast agents on the bronchi and lungs of rats (Ginai et al, 1984). The present work examines the reaction of these agents on the mediastinum of rats.

Nearly half of the deaths (8/18) which occurred in our series appeared to be due to the anaesthetic used before X-ray examination. The exact cause of death in the remaining animals (10 out of 18) is not completely clear. It is however evident (Table I) that deaths are fairly equally divided among various groups, except for the Hytrast group, where no deaths occurred. The Hytrast group, however, produced the highest intensity of reaction. The tissue reaction in the rats who died (Table I) was no different from that of other rats of the same group sacrificed at the same time. This suggests that the contrast agents are an unlikely cause of the deaths.

The mediastinum as such is anatomically complex and difficult to evaluate since it is not always possible to differentiate between the different fascial planes and compartments. Heitzman (1977) described the

mediastinal anatomy and referred to the work of Marchand (1951), who attempted to clarify the anatomy of the fascial planes. According to the description of these authors, "The key to the understanding of the fascial planes of the mediastinum is the concept that the trachea and the oesophagus are enveloped in a loose connective tissue sheath termed the perivisceral fascia". The perivisceral fascia was given this designation by Marchand because it contains the trachea and oesophagus. Around these structures there is a potential space called the visceral compartment of the mediastinum which is continuous cephalad with the fascial planes of the neck. Caudally, the perivisceral fascia is continuous anteriorly with the fibrous pericardium at the bifurcation of the trachea and posteriorly with the aortic adventitia. The mediastinal visceral compartment is crossed at random by connective tissue septa, some of which are continuous with the adventitia of the aorta. Behind the perivisceral fascia is the tough prevertebral fascia which separates the visceral compartment from the paravertebral tissues (Heitzman, 1977). According to Heitzman, after spontaneous rupture of the oesophagus, fluid contents first enter the perivisceral compartment and may then extend into the neck. Marchand (1951) pointed out in the description of his experimental work that the fluid in the mediastinal visceral compartment only collected in those areas where the subfascial connective tissue is sufficiently lax to constitute a potential space. Also the penetration of the fluid through the perivisceral space is further limited by firm attachment of the perivisceral fascia to an underlying structure.

The exact anatomical differences between human and rat mediastinal fascia cannot be defined on the basis of our present experimental work and a search of the literature has not helped in this respect. Why most of

the contrast medium in our series remained limited to the upper part of the mediastinum is not fully explainable. One possibility, as also pointed out by Marchand, would be that the perivisceral fascia in the lower mediastinum may be too firmly attached to the oesophagus and descending aorta, thus leaving no potential perivisceral space for fluid penetration. The close relation of the pleura and pericardium to the perivisceral fascia led to a few inadvertent punctures of these during injection of contrast medium into the mediastinum.

Hytrast appears to produce the most severe inflammatory reaction in the mediastinum and it remained visible on radiographs even at 42 days. This crystalline contrast agent was also clearly visible in the mediastinum histologically.

Barium sulphate and Micropaque produced highly significant reaction compared to the saline/control group and did not seem to differ significantly. Histologically, pure barium sulphate gave rise to granuloma formation, which has also been described by Vessal (1975) while evaluating Gastrografin and barium in the diagnosis of oesophageal perforations. These contrast agents were visible radiologically and histologically until 42 days, in our series. Except in one rat, where Micropaque produced adhesions and was widely distributed, both barium sulphate and Micropaque were seen to be localised usually around or behind the trachea and oesophagus. This localisation suggests injection of contrast agent within the visceral compartment of the mediastinum.

Dionosil also produced a significant reaction in the mediastinum whereas in the bronchi and lungs reaction is insignificant (Ginai et al, 1984).

Gastrografin is an ionic, water-soluble contrast medium identical to Urografin 76% (meglumine and

sodium diatrizoate), except for the addition of a wetting agent (Tween 80) and a flavouring agent (anise). It has a high osmolality (1900 milliosmol, which is about 6 times that of plasma) but in spite of this Gastrografin appeared to produce no significant reaction in the mediastinum in our series. This is, however, significantly different from the effect in the lungs where its high osmolar gradient tends to produce pulmonary oedema with untoward or possibly fatal reaction (Ansell, 1968; Reich, 1969; Frech, 1970; Margulis & Burhenne, 1973). Our study on the bronchi and lung of rats (Ginai et al, 1984), also showed a significant reaction with even small quantities of Gastrografin.

Amipaque produced no significant reactions. This is a non-ionic, water-soluble contrast medium and has theoretically, therefore, half the osmolality of mono-meric ionic agents with identical iodine concentrations. Its osmolality is actually measured to be even less. At a concentration of 370 mg I/ml (equal to the concentration of Gastrografin) Amipaque has approximately double the osmolality of plasma.

Hexabrix also showed no significant reaction in the mediastinum. This is a 2:1 mixture of meglumine and sodium salts of a newly synthesised ioxaglic acid and is a monoacid dimer consisting of two benzine rings to which are attached 6 atoms of iodine. One molecule of the salt in solution dissociates into one cation (sodium or meglumine) and one anion (ioxaglate radicle, containing 6 atoms of iodine) (Grainger, 1981). At a concentration of 320 mg I/ml Hexabrix has an osmolality of 580 milliosmol/kg water, which is approximately twice as much as that of plasma.

The water-soluble contrast media Amipaque, Hexabrix and Gastrografin produced an insignificant tissue reaction in the mediastinum of rats as compared to the saline/control group. However, the possibility of a significant reaction in the lungs (Ginai et al, 1984), including fatal pulmonary oedema (Ansell, 1968), detracts from the safety of Gastrografin as a contrast agent in the mediastinum. This is particularly so in cases where a strong possibility of inhalation exists, e.g., following recent operation where patients may have to be examined in the supine position with consequent risk of aspiration. Amipaque and Hexabrix, both of which have been proven to be safe in the bronchi and lungs in small quantities (Ginai et al, 1984), and also in the mediastinum in the present experimental study, would therefore appear to be the contrast media of choice in examination of postoperative anastomoses or perforations in the upper gastrointestinal tract with risk of leakage into the mediastinum and/or associated aspiration.

CONCLUSION

Hytrast, pure barium sulphate and Micropaque produced highly significant reaction in the mediastinum of experimental rats. Dionosil also caused significant reaction. All these four contrast agents would therefore be unsuitable for use in the upper gastrointestinal tract where there are possibilities of perforation or leakage of contrast agent outside the gut into the mediastinum. These would include spontaneous or iatrogenic perforations of the oesophagus, postoperative gut anastomosis in neck and mediastinum (e.g., colon interposition, small bowel anastomosis to oesophagus, oesophago-gastric anastomoses), surgery of larynx, oesophago-tracheal/bronchial fistula or oesophagopleural fistula.

Hexabrix, Amipaque and Gastrografin produced only slight or no reaction in the mediastinum and would therefore be suitable in cases of suspected leakage. Gastrografin, however, should be avoided in cases where the possibility of aspiration or broncho-oesophageal fistula may be suspected because of the risk of significant reaction in the lungs (Ginai et al, 1984) which may even prove fatal (Ansell, 1968). As Hexabrix is available in ready-to-use solution and is cheaper than Amipaque, we have already started its use in the X-ray department for the above-mentioned indications and have so far come across no adverse reactions (series yet to be published).

The reaction of contrast agents on the peritoneum is currently being investigated.

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Experimental evaluation of various available contrast agents for use in the gastrointestinal tract in case of suspected leakage

EFFECTS ON PERITONEUM

ABSTRACT

The effects of seven contrast agents were studied on the peritoneum of rats in order to find the most suitable and safe contrast agent in cases where leakage might be expected from the gastrointestinal tract into the peritoneal cavity. Hexabrix appeared to give the least tissue reaction, with Amipaque and Gastrografin in second place (but not significantly different statistically).

The present experimental study was carried out to find the most suitable and safe contrast agent for radiological examinations where leakage outside the gastrointestinal tract may be suspected, particularly postoperatively. The contrast agent in such cases may spill into the peritoneal cavity or pleural space or enter the mediastinum. The medium can also enter the bronchi and lungs, either by direct fistula formation between the gastrointestinal tract (GIT) and the bronchi, or by aspiration.

Contrast medium reactions have already been evaluated in the bronchi and lungs as well as in the mediastinum (Ginai et al, 1984, 1985). This present study describes the effects on the peritoneum of various conventional gastrointestinal and bronchographic contrast media and also of two low-osmolality contrast agents, Amipaque and Hexabrix.

MATERIALS AND METHOD

180 male rats (Wistar strain, outbred stock, WU/Cpb) (Zeist, The Netherlands), weighing between 225 and 343 g, were used. The rats were divided into nine main groups of 20, seven receiving contrast agents (see below) and two control groups (one receiving physiological saline and the other nothing).

1 Pure barium sulphate suspension, 90% w/v

2. Commercial barium sulphate suspension 100% w/v (Micropaque; Laboratories Nicholas Gaillard)

3. Sodium and meglumine diatrizoate 370 mg I/ml (Gastrografin; Schering, Berlin)

4. Aqueous suspension of n-propylester of 3 : 5-diiodo-4-oxopyridin-1-ylacetate (Dionosil; Glaxo Laboratories Ltd., Greenford, Middlesex)

*5. Aqueous suspension of (propyl-2 : 3 diol 3 : 5-diiodo-4-pyridone (NPP) and 3 : 5 diiodo-4-pyridone (DIP) (Hytrast; Guerbet, Paris)

6. Metrizamide in a concentration of 370 mg I/ml (Amipaque; Nyegaard, Oslo)

7. Meglumine and sodium ioxaglate 320 mg I/ml (Hexabrix; Guerbet, Paris)

8. Physiological saline (0.9% sodium chloride solution)

9. Anaesthetic only

Each main group was further divided into five subgroups consisting of four rats each (sacrificed on different days). The rats were anaesthetised with ± 0.15 ml Hypnorm® (fluanisone and phentanyl citrate) and fixed to a rat board. Through a mid-line abdominal incision 1.5 ml (equal to ± 375 ml in a 70 kg man) of one of the contrast agents or physiological saline was injected into the peritoneal cavity with a blunt needle, care being taken to inject in all directions. No attempt was made to sterilise the contrast agents. The abdominal incision was then closed with a surgical clip. The control group received the anaesthetic only.

Radiographs of the rats were taken in the frontal projection including both thorax and abdomen, immediately after the introduction of contrast medium and on the day of sacrifice. In addition the long-surviving animals (42-day group) were X-rayed weekly.

A subgroup of four animals from each main group was sacrificed using an overdose of pentobarbitone at 1 day, 2 days, 4 days, 8 days and 42 days after receiving the peritoneal contrast medium. At dissection, the abdomen was opened via a mid-line incision and a gross examination was carried out. The factors noted on gross examination were: the amount of contrast medium, if present, and its distribution in the abdomen; ascites and its nature, adhesions visible to the naked eye, and any obvious visceral abnormalities. The peritoneal lining of the abdominal wall and diaphragm were examined for any abnormal features and for the presence of contrast medium in the peritoneal cavity, and also in the diaphragmatic and retrosternal lymphatics and mediastinal lymph nodes. The chest was examined generally for any gross abnormalities.

Random tissue biopsies were taken from: the

Address for reprints: Dr. A. Z. Ginai, Department of Radiology, University Hospital Dijkzigt, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.

*This agent is not available in the United Kingdom.

abdominal wall with peritoneal lining (at least four places); diaphragm, greater omentum; mesentery of small bowel; mesocolon; lymph nodes from the anterior mediastinum (one or two). All the tissues removed were immersed in formalin for two weeks before preparing histological sections which were stained with haematoxylin and azophloxin. The following grading system was used for the histological reaction, based primarily on the type and extent of the inflammatory reaction.

    0   normal or no significant reaction
    +   mild reaction
    + +   moderate reaction
    + + + severe reaction

Statistical analysis

The χ^2 test (for k independent samples) was applied for the determination of the level of significance.

RESULTS

All the animals planned to survive 4, 8 and 42 days (12 in total) in the Hytrast group died about 48 hours after introduction of contrast medium. Results from this group are therefore presented separately (Table III). Ten animals died in the remaining groups; seven shortly after anaesthesia for taking radiographs, but in the remaining three no definite cause of death could be established. Dissections were carried out in all animals except three where the condition of the animal did not allow an adequate dissection.

RADIOLOGICAL APPEARANCES

Pure barium sulphate

Contrast medium was all around the intestines, often under the diaphragm and over the liver area and paracolic gutters in the early stages (*i.e.,* immediately after introduction) (Fig. 1). On day 1, some loculation of barium was visible and contrast medium could be seen in the scrotum. On day 2 loculation of barium was seen and the medium was noticeable under the diaphragm and appeared to fill the retrosternal lymphatics and lymph nodes in the superior mediastinum. Lymph-node filling was also noted in the 4-, 8- and 42-day groups and appeared to increase with time. Some abdominal lymph nodes were also filled in the longer-surviving groups. The general appearance of barium in the abdomen changed only slightly up to the 42nd day. The total quantity of contrast medium, however, appeared to be somewhat less than at the beginning.

Micropaque

Appearances were very similar to those with barium sulphate, except that the retrosternal lymphatic channels and lymph nodes contained more contrast medium (Fig. 2). In the later stages, the peritoneal lining was more heavily coated than with the pure barium sulphate group (Fig. 3). Abdominal lymph-node filling was seen on day 4, and more especially from day 8 onwards (Fig. 3).
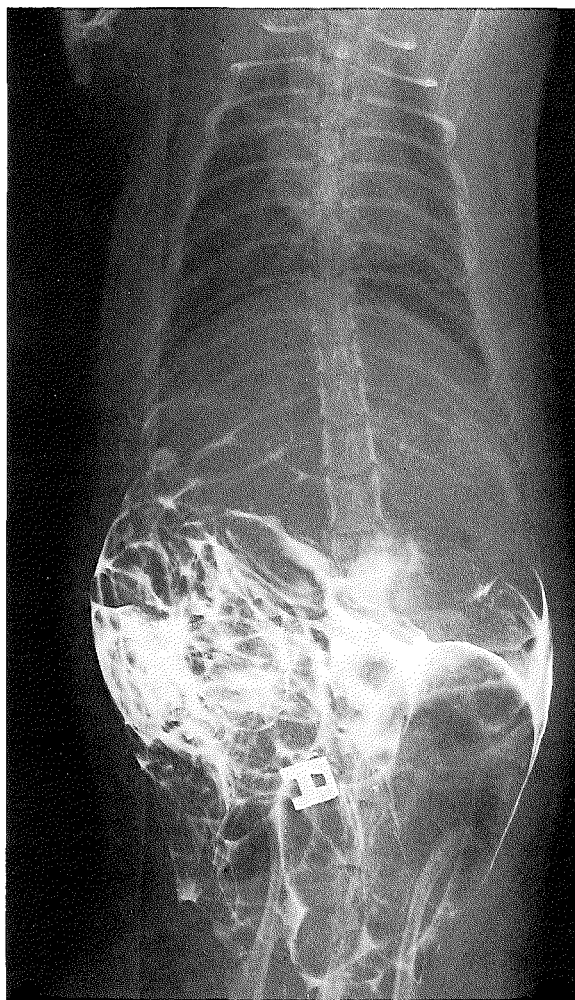

FIG. 1.

Pure barium sulphate immediately after introduction into the peritoneum showing contrast medium spreading between the intestines and in the paracolic gutters.

Hytrast

On the radiographs of the peritoneal cavity taken soon after injection, dense contrast medium was visible around the intestines (Fig. 4). At day 1, loculation was noted and the contrast medium was also visible under the diaphragm, with filling of the retrosternal lymphatic channels and anterior mediastinal lymph nodes (Fig. 5). Loculation of contrast medium was again noted on day 2. The intestines appeared rather distended, with a granular appearance suggestive of uptake by the intestinal walls. The retrosternal lymphatics, anterior mediastinal lymph nodes and a plexus of diaphragmatic lymphatics were filled with contrast medium. All the other rats died about 48 hours after injection; many cadavers were radiographed and showed appearances very similar to those described above for day 2 (Fig. 6).
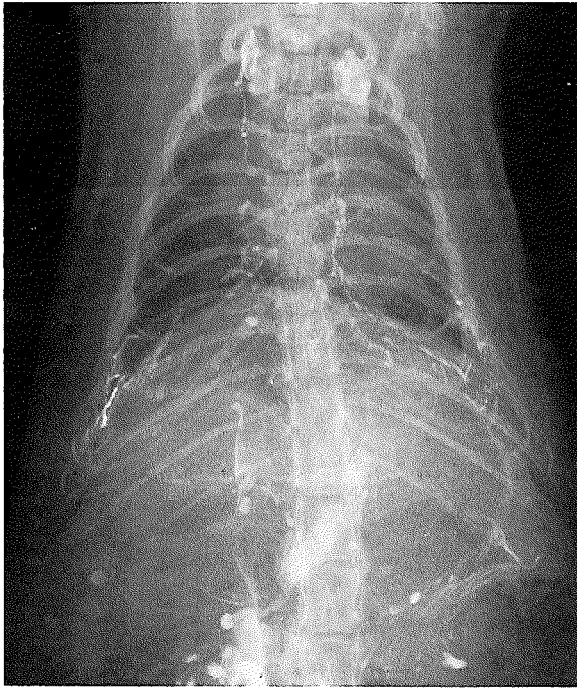
FIG. 2.

Filling of diaphragmatic lymphatics and retrosternal lymphatic channels and lymph nodes with Micropaque is well shown on a 4-day radiograph.

Dionosil

The contrast medium could be seen around the intestines and paracolic gutters, over the liver and under the diaphragm on radiographs taken immediately after introduction. On day 1, very small quantities of loculated contrast medium were visible in the abdomen, on day 2 only tiny residues, and from day 4 onwards no contrast medium was visible and no abnormalities were noted. Retrosternal lymphatics and lymph nodes were not opacified.

Amipaque

Radiographs taken immediately after injection showed contrast medium all around the intestines and paracolic gutters, under the diaphragm, over the liver and in the scrotum. From day 1 till day 42 no contrast medium was visible in the abdomen. No opacification of lymphatics of lymph nodes was noted in the thorax.

Gastrografin

Appearances were similar to those for Amipaque.

Hexabrix

Here too appearances were similar to those for Amipaque (Fig. 7).
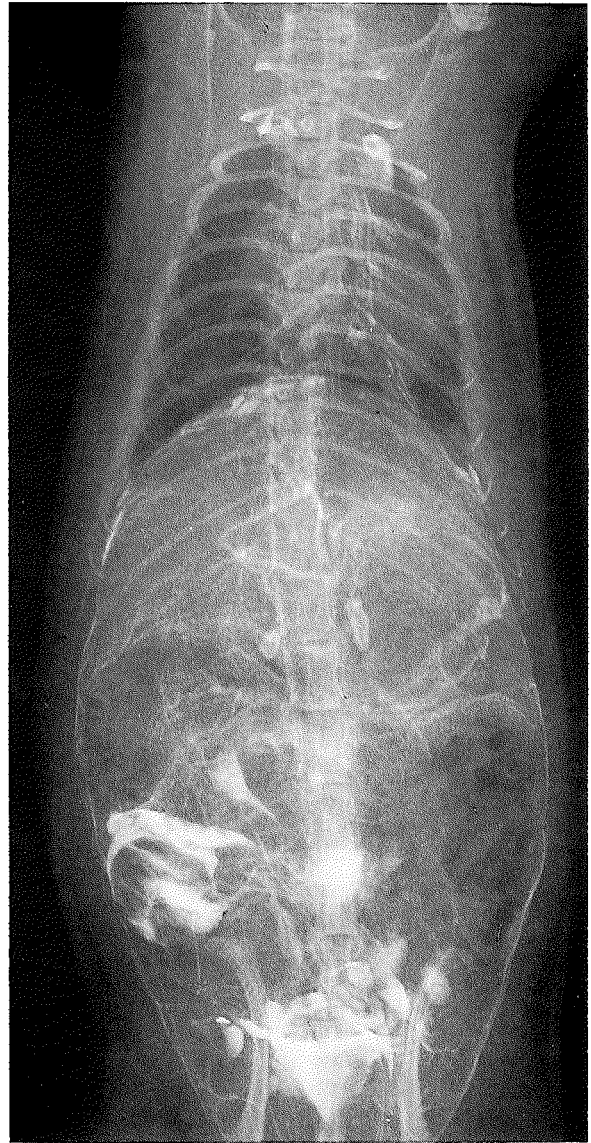
FIG. 3.

A 42-day radiograph showing well coated peritoneal lining of the abdomen with Micropaque. Filling of the diaphragmatic and retrosternal lymphatics and mediastinal lymph nodes; two abdominal lymph nodes are also filled with contrast.

Physiological saline and control groups

No specific abnormalities were seen in these groups.

PATHOLOGICAL OBSERVATIONS

Gross examination

The pure barium sulphate, Micropaque and Hytrast groups all showed a whitening, which was particularly notable in the greater omentum and mesentery, over the surface of the liver and on the peritoneal surface of the
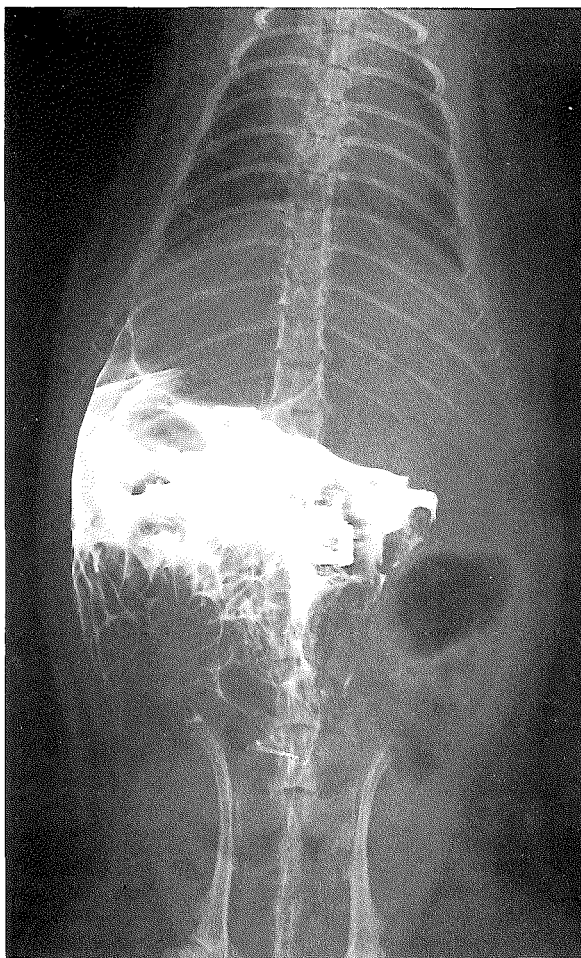
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FIG. 4.

Radiographs taken immediately after introduction of Hytrast in the abdomen.
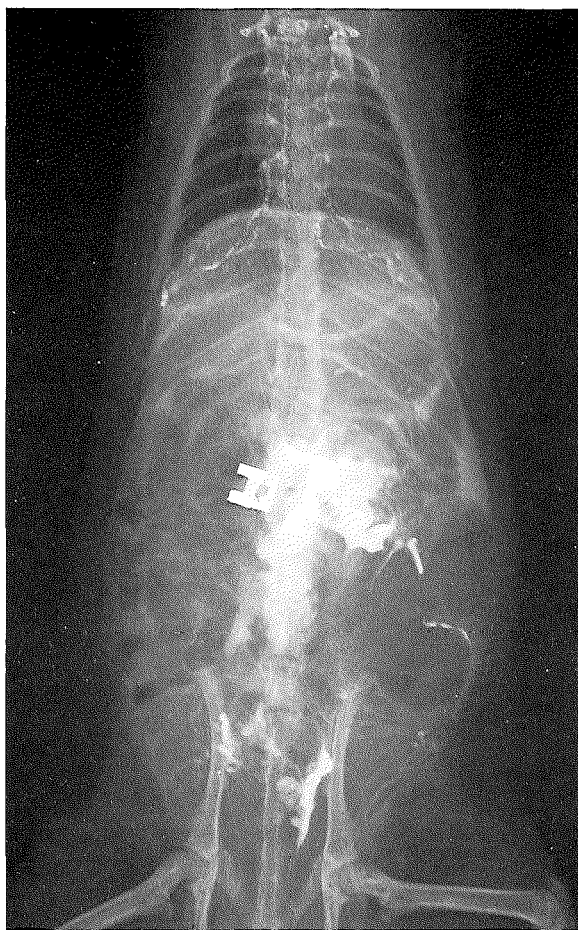

FIG. 5.

X-ray taken at 24 hours (1 day) shows Hytrast to be loculating mainly in the centre of the abdomen. Distended loops of bowel are seen. Marked filling of diaphragmatic lymphatics and retrosternal lymphatics and lymph nodes is already visible.

diaphragm in most animals. Some free contrast medium could be seen in the peritoneal cavity on the first and second day. Later, pure barium sulphate and Micropaque tended to clump in various regions on the peritoneal surface to which they apparently adhered. The results for the Hytrast series are not totally comparable as all animals in 4-, 8- and 42-day groups died on the second day.

The incidence of ascites is shown in Table I. Pure barium sulphate and Micropaque showed greyish ascites; the Hytrast group showed at first green stained and later brown stained ascites. The incidence of peritoneal adhesions visible to the naked eye is shown in Table II. No clear bowel distension or obstruction was observed in the pure barium sulphate and Micropaque groups, but the Hytrast group showed bowel distension with some contrast medium within the bowel wall in the day 2 group and in many of the

animals who died. Pleural effusion was also noted in several rats in the Hytrast group.

The contrast medium was also seen in the diaphragmatic and restrosternal lymphatics, as well as lymph nodes in the anterior mediastinum, in the Hytrast, Micropaque and pure barium sulphate groups. In the later two, good filling of the lymph nodes was still visible at 42 days.

No ascites, adhesions or lymphatic filling with contrast medium were observed in the Amipaque, Gastrografin, Hexabrix or Dionosil groups and no other gross abnormalities were noted in these animals at autopsy.

HISTOLOGICAL REACTION

Pure barium sulphate

On day 1 the contrast medium was mainly on the surface of the tissues. On day 2 the peritoneal lining was
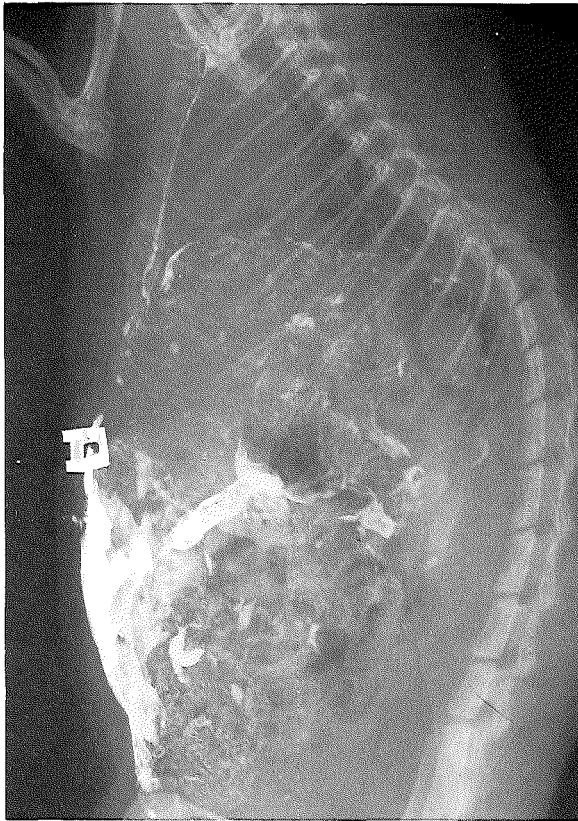
FIG. 6.

Lateral radiograph of a dead rat at 2 days after introduction of Hytrast into the peritoneum. Dense collections are seen particularly anteriorly with some possibly in the bowel. Filling of diaphragmatic and retrosternal lymphatics and lymph nodes is also visible.
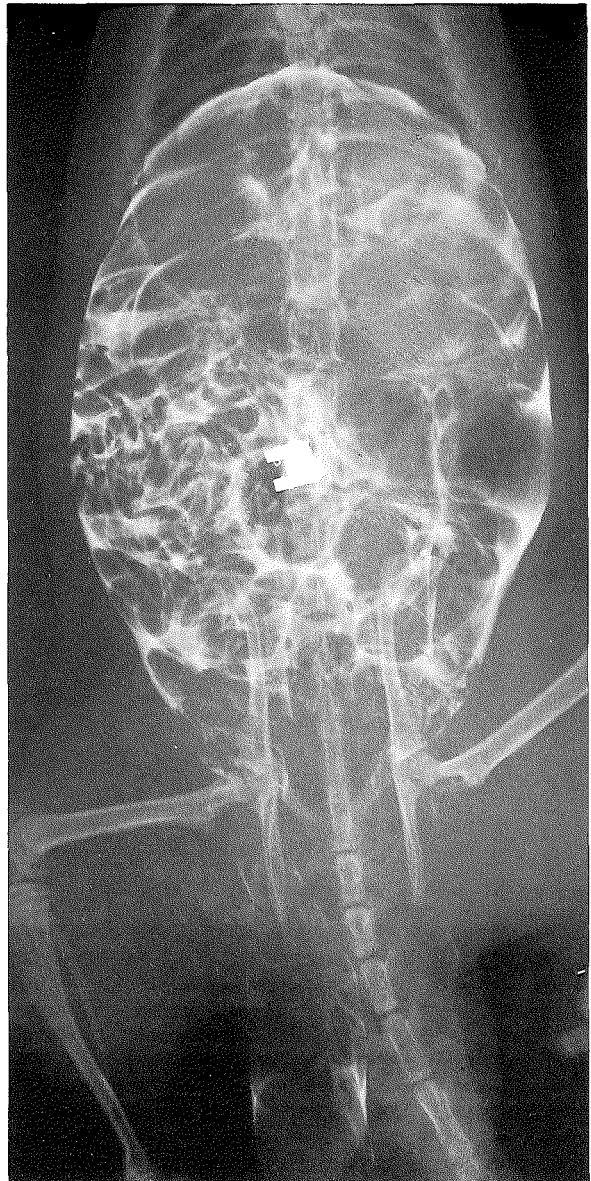

FIG. 7.

X-ray taken immediately after intraperitoneal Hexabrix injection. The contrast medium is seen around the intestines, paracolic gutter, scrotum and under the diaphragm.

swollen with accumulation of contrast in the lining cells and macrophages. At day 4 an extensive histiocytic reaction was noted beneath the peritoneal lining and by then contrast medium was found to be in the cytoplasm of the histiocytic cells. At 8 and 42 days, fibroblastic reactions surrounded by histiocytic cells and multinuclear foreign body giant cells were noted (Fig. 8A, B). Contrast medium was also seen on the second day in the dilated sinusoids of mediastinal lymph nodes. On the fourth day it was seen in the histiocytic cells, mainly in sinusoids of the lymph nodes. At 42 days the lymph nodes consisted solely of histiocytic cells full of contrast medium (Fig. 9).

Micropaque

On days 1 and 2 extensive deposits of contrast medium were seen, surrounded by a slight histiocytic reaction. At this stage the contrast medium was mostly extracellular and on the surface. By 4, 8 and 42 days it was diffusely spread in the tissues, mainly within the

cytoplasm of the histiocytic cells. Some lymphocytes, polymorphonuclear leucocytes and minimal fibrosis were also seen. In the mediastinal lymph nodes, contrast medium was mainly in the histiocytic cells lying in the sinusoids.

Hytrast

All the animals died on the second day, and showed similar histological reactions consisting of a necrotising

TABLE I

Ascites as seen at autopsy

Day of dissection	1	2	4	8	42
Barium sulphate (pure)	+++	++	+++	O	O
	++	++	++	O	O
	+	++	++	O	O
	+	+	O	O	O
Micropaque	++	+	++	++	O
	++	+	++	++	O
	+	+	++†	++	O
	+	+	+	O	O
Hytrast	+	++	++*	+*	++*
	+	+	++	+	++
	+	+	++	+	++
	+	O	+	×	+

O = No ascites
+ = Mild ascites
++ = Moderate ascites
+++ = Severe ascites
Dionosil, Gastrografin, Amipaque, Hexabrix, Physiologic Saline and control groups showed no ascites at autopsy
* = All animals in these groups died on 2nd day
† = Animal died
× = Dissection not carried out

inflammatory process with fibrin, polymorphonuclear cells and nuclear dust in all tissues examined (Fig. 10). In the lymph nodes, too, a necrotising purulent material was noted mainly in the sinusoids. Crystalline contrast material was recognisable in various tissues.

TABLE II

Adhesions as visible on gross examination

Day of dissection	1	2	4	8	42
Barium sulphate (pure)	O	O	O	+	O
	O	O	+	++	O
	O	O	+	++	+
	O	O	+	++	+
Micropaque	O	O	O	+	O
	O	O	O	+	O
	O	O	+†	++	O
	O	O	+	++	O
Hytrast	O	O	O*	O*	O*
	O	O	O	+	O
	O	O	O	+	O
	O	O	+	×	O

O = No adhesions
+ = Moderate adhesions
++ = Extensive adhesions
* = All animals in these groups died on 2nd day
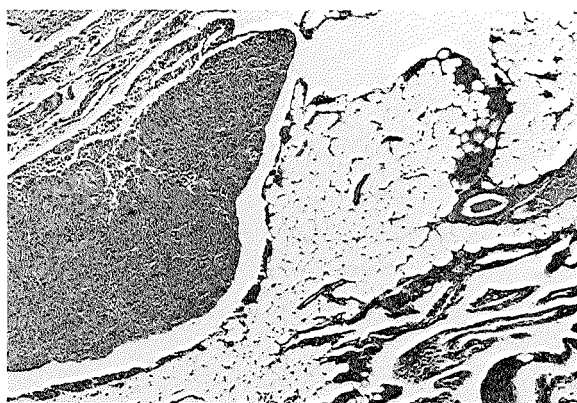† = Animal died
× = Dissection not carried out

FIG. 8A.

Histological section showing circumscribed accumulation of barium sulphate at 42 days in the region of mesentery of small bowel. (Haematoxylin and azophloxin (H and A) 60 ×).
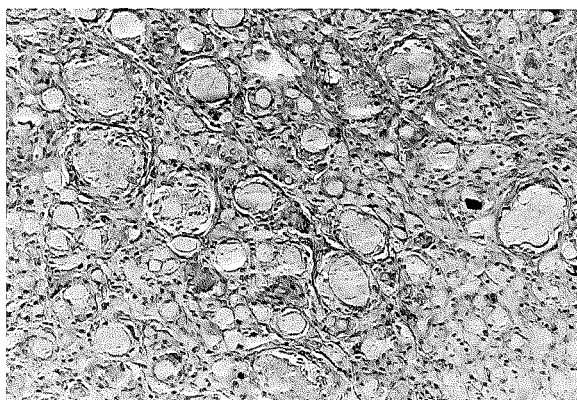

FIG. 8B.

In higher magnification the contrast barium sulphate is seen within the histiocytes with formation of giant cells in some places. (H and A 150 ×).

Dionosil

There was an acute inflammatory reaction at first with fibrinoid exudate, some proliferation of mesothelial cells and an increase in mast cells. In later stages a mild, inflammatory reaction consisting of lymphocytes and histiocytes was seen. Lymph nodes also showed fibrinous histiocytosis and a remarkable increase in mast cells.

Gastrografin

A slight reaction was seen, with lymphocytes and histiocytes and some irritation of mesothelial cells (Fig. 11). There was an increase in mast cells and lymph nodes showed sinus histiocytosis.
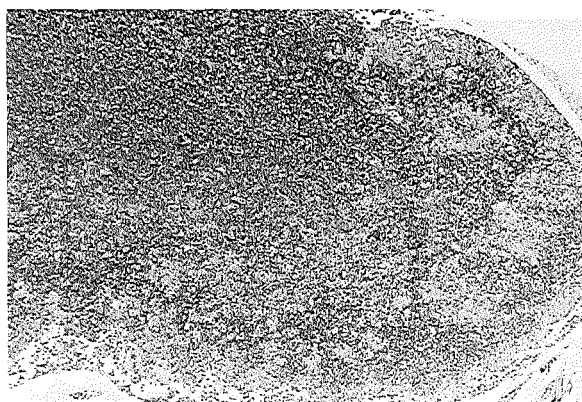
FIG. 9.

Histological section showing barium sulphate in a mediastinal lymph node at 4 days after peritoneal injection. The contrast medium is visible focally with the lymph node and also the marginal sinus. (H and A 60 ×).
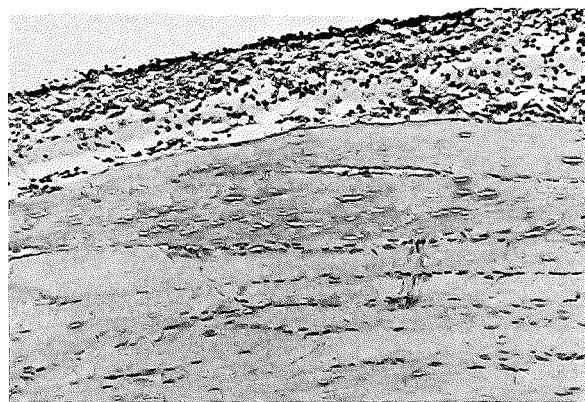

FIG. 11.

Microscopic view showing diffuse inflammatory infiltrate in the peritoneal lining of the abdominal wall 2 days after intraperitoneal Gastrografin (H and A 150 ×).

Amipaque

Slight focal lympho-histiocytic reaction was seen in the various tissues of the peritoneum. Lymph nodes showed follicular hyperplasia.

Hexabrix

Minimal reaction, but with extensive increase in mast cells, was noted in several places in the tissues examined.

Physiological saline

Minimum reaction was seen with a few lymphocytes and polymorphs; some swollen mesothelial cells were present.

Anaesthetic only

A few mast cells and lymphocytes were present in peritoneal and mesenteric tissues.

Table III summarises the histological grading for all rats. The Hytrast group was excluded in the statistical analysis as all animals not previously sacrificed had died on about day 2. The χ^2 test showed a significant difference between the various groups ($p < 0.001$). As the physiological saline and anaesthetic only groups did not differ, they were combined to form a single group. Pure barium sulphate, Micropaque and Dionosil showed a highly significant reaction as compared to the combined control group ($p < 0.001$). Amipaque and Gastrografin gave an insignificant reaction as compared to the control group. Hexabrix did not show a significant difference compared to the control group.

FIG. 10.

Microscopic view showing localised, necrotising, inflammatory reaction in the region of the omentum 2 days after intraperitoneal injection of Hytrast. The medium is seen as dark areas in the region of necrosis.

DISCUSSION

These results form part of an experimental study carried out to find a safe and radiographically suitable contrast agent for use in the gastrointestinal tract in cases where it might be expected to leak into the mediastinum, lungs, pleura or peritoneum (depending upon the route of examination and the area being examined). It was decided to study various available conventional gastrointestinal and bronchographic contrast agents and compare them with the comparatively new, low-osmolality water-soluble agent Hexabrix and nonionic Amipaque. Gastrografin was also included because it is known to have caused fatal incidents after aspiration into the lungs (Ansell, 1968; Chiu & Gambach, 1974). The reactions in the bronchi and lungs (Ginai et al, 1984) and on the mediastinum (Ginai et al, 1985) have already been evaluated.

The present study has shown that Hytrast in the quantities used in the peritoneum of rats, was consistently lethal, causing death in two days of all

animals not already sacrificed. Hytrast, introduced as a bronchographic contrast medium in 1962, is a neutral suspension of crystals of N-(propyl-2 : 3-diol)-3 : 5 diiodo-4-pyridone and 3 : 5 diiodo-4-pyridone in a

TABLE III

TISSUE REACTION IN THE PERITONEUM OF 180 RATS

Day of dissection	1	2	4	8	42	Total
Barium sulphate (pure)	++	+	+++	+++	+++	
	+	+	++	+++	++	39°
	+	+	++	+++	++	
	+	+	++	+++	++	
Micropaque	+	+++	+++	+++	+++	
	+	++	++	+++	+++	41°
	+	++	+†	+++	++	
	+	+	+	+++	++	
Dionosil	++	++	++	++	++	
	++	+	+	+	+†	23°
	+	+	+	+†	O	
	+	O	+	+	O	
Gastrografin	+	++	++	++	++	
	+	+	+	++	+	18
	O†	O	+	+	+†	
	O	O	×	+	O	
Amipaque	+	++	++	+	+	
	+	+	++	O†	+	18
	+†	+	+	O	+	
	O	+	O	O	+	
Hexabrix	++	+	+	++	+	
	+	O	O	++	+	13
	+	O	O	+	O	
	O	O	O	O	O	
Physiologic saline	+	O	O	++	+	
	O	O	O	+	O†	6
	O	O	O	+	O†	
	O	O	O	×	O	
Control	+	+	O	+	+	
	+	O	O	+	+	7
	O	O	O	O	O†	
	O	O	O	O	O	
Hytrast	+++	+++	+++*	+++*	+++*	
	+++	+++	+++	+++	+++	
	+++	+++	++	+	+++	52
	+++	+++	+	×	+++	
Total	27	26	31	47	35	

O = No significant reaction
+ = Mild reaction
+ + = Moderate reaction
+ + + = Severe reaction
* = All animals in these groups died on about the 2nd day. Hytrast group was therefore totally excluded from the statistical analysis
† = Deaths
× = Dissection not carried out
° = p < 001 between all groups
p < 001 compared to physiological saline/control group

hypertonic aqueous solution of sodium carboxymethylcellulose (Morley, 1969). The viscosity varies from 6 poises (French preparation) to 2.4 poises (American preparation) at 37°C, depending on the quantity of methyl cellulose used in its preparation (Grainger et al, 1970). Although Hytrast gives excellent quality bronchograms, it is known to have produced significant reactions in the lungs both in animals (Greenberg, 1964; Ginai et al, 1984) and in humans. Thirty-eight cases of severe reactions (including one death) were reported by Agee and Shires (1965). Misener et al (1965) observed pyrexia in 66% of their patients after Hytrast bronchography compared to 16% after the use of Dionosil. "Hytrast is capable of inducing crystalline inclusion pneumonia in animals and humans", according to Cabrera et al (1967).

All animals given Hytrast in this study and not already sacrificed died about two days after its introduction into the peritoneum and it was obvious, clinically, that the material was very toxic. On autopsy the contrast agent was seen as whitish clumps, particularly over the greater omentum, liver and mesentery of the small bowel; very few adhesions were noted. Many rats showed distended bowel loops and in some instances contrast medium appeared to be in the intestinal wall. Ascites was always present and had a brownish appearance. The lymphatic plexus in the diaphragm, retrosternal lymphatics and anterior mediastinal lymph nodes were filled in all the animals in the Hytrast group. The exact cause of death in this group is not known and study of the literature does not help in this regard.

Barium sulphate in various commercial preparations is the contrast medium of choice for the examination of the gastrointestinal tract. This is because of its superb radiographic density, low toxicity and low cost. The adverse effects of leakage into the peritoneal cavity are, however well described in the literature. In 1916 Rosenthal reported the first case of barium peritonitis from perforation of an acute duodenal ulcer immediately after a barium meal study (cited by Surg et al, 1977). Since that time various reports of this complication have appeared in the literature. Cochran et al (1963) experimentally assessed the complications arising from spillage of both pure and commercial barium sulphate into the peritoneal cavity, studying their effects alone and in combination with sterile and unsterile faeces in 29 dogs. Their results showed that barium sulphate had an adverse effect on the peritoneum and all animals who lived long enough developed granulomas. They also suggested that commercial barium sulphate was more harmful than pure barium sulphate and that the combination of commercial barium sulphate and unsterile faeces was more harmful than either of them alone. This confirms the well known fact that infection is aggravated by the presence of foreign material. In the present experiment, the effects of pure barium sulphate and of Micropaque did not differ greatly as regards ascites, adhesions or

histology (Tables I–III). The peritoneum appeared to be more densely coated in the later stages in the Micropaque group, possibly as a result of the coating agents in Micropaque (Fig. 3). No intestinal obstructions were encountered in either group and adhesions could not be recognised by the naked eye at 42 days. As this experiment was carried out only to demonstrate the tissue reaction to contrast media, no perforation or faecal contamination was induced in our experiments. Several series have already been published showing harmful effects of faecal contamination on the peritoneum (Cochran et al, 1963; Sisel et al, 1972).

According to Herrington (1965), if barium remains in the peritoneal cavity, a chronic granuloma results in which a thick plaque of dense fibrous tissue may encase vital structures. Kay and Choy (1955) studied the histological reaction of barium sulphate on the peritoneum of mice. They showed that a severer tissue reaction was noted with larger quantities of contrast medium and that adhesions were seen as early as 4 days with simultaneous small granuloma formation. Our pathological observations are very similar to these.

Lymphatic opacification of the diaphragmatic lymphatic plexus, restrosternal lymphatics and lymph nodes was noted in the pure barium sulphate, Micropaque and Hytrast groups. The barium sulphate and Micropaque groups also showed filling of a few of the abdominal lymph nodes, probably retroperitoneal, in the longer surviving groups. Berdon et al (1973) described two babies who survived barium peritonitis from colon perforation with subsequent visualisation of retrosternal lymphatics. Koehler and Rodriguez (1968) have shown by their experimental work on different animals including rats that "intraperitoneal injections of a suitable contrast agent will result in opacification of substernal nodes in the laboratory animals". In some species retroperitoneal and/or mesenteric nodes may also be visualised. They found that a particle size of 1–4 μ was the most suitable for lymphatic absorption.

Dionosil produced a significant reaction as compared to the control groups but no ascites or adhesions were noted.

Amipaque, Gastrografin and Hexabrix produced insignificant reaction compared with the control groups, with Hexabrix causing the least reaction.

Gastrografin is a conventional water-soluble gastrointestinal contrast agent identical to Urografin 76% (meglumine-sodium diatrizoate) with the addition of flavouring (anise) and a wetting agent (Tween 80). It is highly hypertonic with an osmolality about six times that of blood.

Amipaque is non-ionic and therefore has half the osmolality of monomeric ionic agents (or even less). A concentration equal to that of Gastrografin (370 mg I/ml) has about double the osmolality of blood.

Hexabrix is a 2 : 1 mixture of meglumine and sodium salts of ioxaglic acid which is a monoacid dimer and consists of two benzene rings to which are attached 6 atoms of iodine. At a concentration of 320 mg I/ml

Hexabrix has an osmolality approximately twice that of blood (Grainger, 1979).

In this experimental study, where the contrast medium was injected directly into the peritoneal cavity, osmolality (in the doses used) did not appear to influence the general reaction, as shown by the insignificant difference between Gastrografin, Amipaque and Hexabrix (Table III). Personal experience as well as study of the literature have shown that Gastrografin and similar monomeric high-osmolality contrast media have several disadvantages when used in the gastrointestinal tract. According to Cohen et al (1980), the hypertonicity and hyperosmolality of water-soluble iodinated contrast media (e.g., Gastrografin) caused them to be rapidly diluted, with resulting poor visualisation of the small and large bowel on follow through examination. Moreover, they are potentially toxic to bowel mucosa (Lutzger & Factor, 1976). Thirdly, because they draw water from body tissues into bowel lumen, they may cause fluid shifts which may be extremely harmful, especially to infants and small children (Johansen & Kolmannskog, 1978). Fourthly, and perhaps most important of all, they are extremely toxic if aspirated and should be used with caution in proximal bowel obstruction or vomiting, potential fistula to lung or disordered swallowing (Johansen & Kolmannskog, 1978; Chiu & Gambach, 1974). Another disadvantage of these contrast agents is that they can be precipitated by gastric hydrochloric acid, according to Johansen & Kolmannskog (1978); these authors also state that isotonic metrizamide (Amipaque) overcomes all the disadvantages of Gastrografin, and therefore advocate the use of metrizamide in all circumstances where both barium sulphate and Gastrografin would be contraindicated, particularly in children. The use of Hexabrix in the paediatric gastrointestinal tract has also been recently reported by Ratcliffe (1983). Our experimental results suggest that Hexabrix and Amipaque would be the contrast media of choice in any circumstances where leakage outside the gastrointestinal tract into the peritoneal cavity might occur. It also appears to be particularly important in the upper gastrointestinal tract where there is possible danger of aspiration.

CONCLUSION

Tissue reactions in the peritoneum were studied experimentally using seven contrast agents: Dionosil, Gastrografin, Hytrast, Micropaque and pure barium sulphate and two low-osmolality contrast agents, Amipaque and Hexabrix. Pure barium sulphate and Micropaque caused severe reaction with ascites due to peritonitis and adhesions and a highly significant histological reaction (Table III). Dionosil also caused a significant reaction in the peritoneum. Hytrast caused death of all animals on about the second day. Hexabrix produced the smallest reaction, closely followed by Amipaque and Gastrografin. There is no significant difference between these three contrast agents. It would

however appear from the experimental studies on the lungs (Ginai et al, 1984) that in examination of postoperative patients with surgery of the upper gastrointestinal tract where there is danger of aspiration or intraperitoneal leakage, Hexabrix or Amipaque would be safer. For these reasons Hexabrix has been used in our radiological department for over two years for examination of the upper gastrointestinal tract in cases where leakage is suspected, particularly postoperatively.

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Experimental evaluation of various available contrast agents for use in the gastrointestinal tract in case of suspected leakage

EFFECTS ON PLEURA

ABSTRACT

Intrapleural injections of seven contrast agents were carried out in experimental rats in order to find a safe contrast agent to use in the radiological examination of the upper gastrointestinal tract in cases where leakage outside the upper gastrointestinal tract into the pleural space could be suspected, particularly post-operatively. The contrast agent in such cases could enter the mediastinum, pleura, peritoneum or lungs and bronchi. Hexabrix (May and Baker) and Gastrografin (Schering AG) produced the least tissue reaction in the pleura. Due to the potential risk of aspiration in such cases Gastrografin is not suitable as it is known to produce significant reaction in the lungs and may even prove to be fatal. Hexabrix, therefore, appears to be the safest contrast agent where leakage into the pleural space may be suspected.

Experimental work was carried out to find a safe and suitable contrast agent for use in the gastrointestinal tract in cases where leakage outside the tract could be suspected, particularly post-operatively. The contrast agent used in the radiological evaluation of such cases can enter the mediastinum, pleura, or peritoneum, or be aspirated into the bronchi and lungs, or enter the lungs via a fistula. The reactions of various conventional gastrointestinal and bronchographic contrast agents as well as the more recent low-osmolality contrast agents metrizamide (Amipaque, Nycomed (UK) Ltd) and Hexabrix (May and Baker) have already been studied in the bronchi and lungs (Ginai et al, 1984), mediastinum (Ginai et al, 1985) and peritoneum (Ginai, 1985). This paper presents the effects of various contrast agents on the pleura of rats. Amipaque, which was used in the previous studies on lungs, mediastinum and peritoneum, is now replaced by iohexol (Omnipaque, Nycomed (UK) Ltd).

MATERIALS AND METHOD

One hundred and eight male rats (Wistar Strain, outbred stock, wu/cpb (Zeist, The Netherlands)), weighing between 264 g and 395 g were used. The rats were divided into nine main groups of 12 rats, seven groups receiving contrast agents (see below) and two

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control groups, one receiving physiological saline and the other anaesthetic only.

(1) Pure barium sulphate $\sim 90\%$ weight/volume (w/v) suspension.

(2) Micropaque, commercial barium sulphate suspension 100% w/v (Laboratories Nicholas Gaillard).

(3) Gastrografin, sodium and meglumine diatrizoate 370 mg I/ml (Schering AG, Berlin).

(4) Dionosil, aqueous suspension of n-propylester of 3 : 5-diiodo-4-oxopyridin-1-ylacetate (Glaxo Laboratories Ltd, Greenford, Middlesex).

(5) Hytrast, aqueous suspension of N-propyl-2 : 3 diol 3 : 5-diiodo-4-pyridone (NPP) and 3 : 5 diiodo-4-pyridone (DIP) (Guerbet Laboratories, Paris).

(6) Omnipaque, iohexol in a concentration of 350 mg I/ml (Nycomed (UK) Ltd).

(7) Hexabrix, meglumine and sodium ioxaglate 320 mg I/ml (May and Baker, Dagenham).

(8) Physiological saline, 0.9% sodium chloride solution.

(9) Control, anaesthetic only.

Each main group was further divided into three subgroups of four rats according to the day of sacrifice (1 day, 8 days and 42 days). The rats were anaesthetised with ether and then placed on a rat board. A small incision was made on the left chest wall laterally, usually between the fifth and the sixth ribs obliquely in the line of the ribs. The chest wall and intercostal muscles were carefully dissected until the parietal pleura was reached. Through a small opening in the pleura, which always caused an immediate pneumothorax, 0.2 ml (equal to ~ 45 ml in a 70 kg man) of one of the contrast agents or physiological saline was injected using a blunt polyethylene catheter. Immediately following the injection, the opening in the chest wall was closed with two or three layers of stitches. Radiographs of the chest were taken in the postero-anterior and lateral positions immediately after the injection and again on the day of sacrifice. In addition, radiographs were taken on Days 2 and 4 in the 8-day group and Days 7, 14 and 28 in the 42-day group. Subgroups of four animals from each main group were sacrificed (using an overdose of ether) at 1 day, 8 days and 42 days after receiving the contrast agent or saline. At dissection, the chest was carefully opened on both

sides and examined for the presence and distribution of contrast agent, any pleural effusion present and any gross abnormalities of the lungs, mediastinum, diaphragm and chest wall. Biopsies were taken from both sides of the chest and consisted of: (a) at least two biopsies of the intercostal muscle with parietal pleural lining chosen randomly but excluding the region of surgery when visible; (b) the diaphragm; (c) the infracardiac mediastinal tissue consisting of a loose fatty type of tissue with pleural lining; and (d) sections from both lungs with visceral pleural lining. In addition, lymph nodes (paratracheal and anterior mediastinal where possible) in the 8-day and 42-day groups were also removed. All these tissues were immersed in formalin for about 2–4 weeks, after which histological sections were prepared and stained with haematoxylin and azophloxin. The histological evaluation was based on the type and severity of the inflammatory reaction. The presence or absence of contrast agent was also noted.

The histological reaction in the pleura was graded as follows: 0 no reaction; + mild reaction; + + moderate reaction; + + + severe reaction. The χ^2 test (for K independent samples) was applied for the determination of the level of significance.

RESULTS

The animals, in general, tolerated the anaesthetic and the surgical procedure quite well. There were three deaths in total, all occurring following anaesthesia, before X-ray examination (see Table I). The general complications of surgery included three rib fractures, which healed well, and a total of nine animals in which the left lung was caught in the inner layer of chest wall stiches. In these animals adhesions were also seen between the left lung and the chest wall at the site of introduction of the contrast agent.

Radiological findings

All contrast agents were clearly visible on the chest radiographs taken immediately after injection. Despite the care taken to inject only into the left pleural space, the contrast agent was most often seen in both pleural spaces (Fig. 1A), sometimes only on the left side (Fig. 1B) but sometimes mainly on the right side (Fig. 1C). At this stage, pneumothorax was always present on the left side (Fig. 1). In the case of Omnipaque, Hexabrix, Gastrografin and Dionosil, the agent appeared to be almost completely absorbed after 24 h and in these groups, as well as the physiological saline group, there was no demonstrable pneumothorax on the 24 h radiographs. No recognisable collapse, consolidation or pleural effusion could be seen in these groups up to the 42nd day.

The pure barium sulphate, Micropaque and Hytrast groups showed definite localisation of the contrast agents in the region of the mediastinum, mainly to the left and anteriorly. Only very slight variatio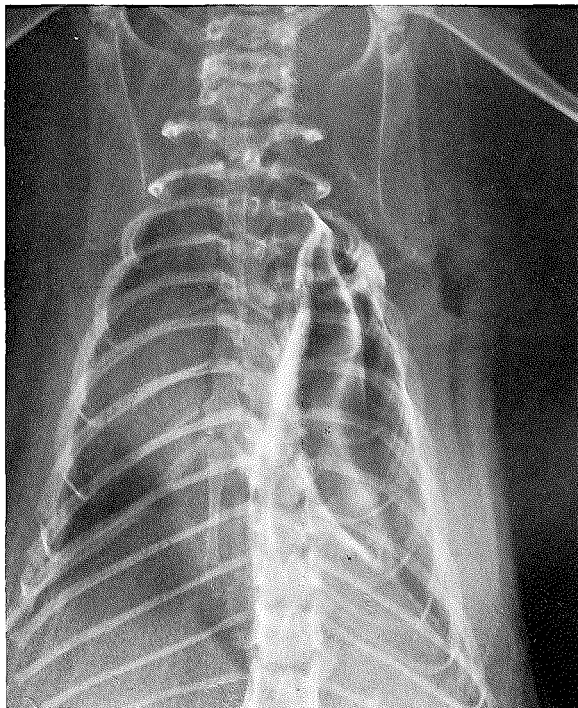ns were seen up to the 42nd day in the pure barium sulphate and Micropaque groups (Fig. 2). The Hytrast group, however, showed only a tiny amount of residual contrast agent by the 42nd day. These three groups (pure barium sulphate, Micropaque and Hytrast) also appeared to have some pleural effusion on Day 1 and in some cases until Day 8. A small pneumothorax was also seen in many animals in these groups until this time. No contrast-filled lymph nodes could be defined in the mediastinal region on radiographs, but small areas suggestive of collapse/consolidation of the lungs were visible in some rats in all three groups.
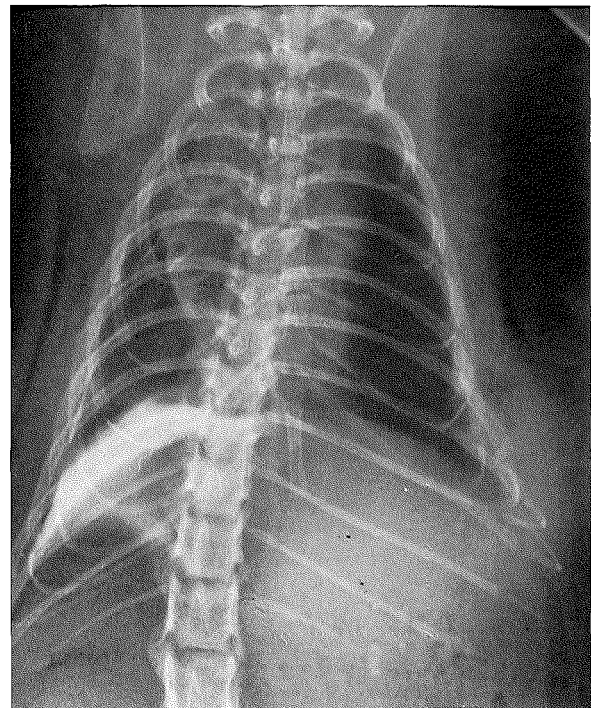
TABLE I

TISSUE REACTION IN THE PLEURA OF 108 RATS

Agent	Day of dissection			Total
	1	8	42	
Pure barium sulphate	+ +	+ + +	+ +	26
	+ +	+ + +	+ +	
	+ +	+ + +	−	
	+ +	+ + +	+ +*	
Micropaque	+ + +	+ + +	+ + +	33
	+ + +	+ + +	+ + +	
	+ +	+ +	+ + +	
	+ + +	+ +*	+ + +	
Hytrast	+ + +	+ +	+	23
	+ + +	+ +	+	
	+ + +	+ +	+	
	+ + +	+ +*	0	
Dionosil	+	+ +	+	11
	+	+	+	
	+	+	0	
	+	+	0	
Gastrografin	+	+ +	+	10
	+	+ +	+	
	+	+	0	
	0	0	0	
Omnipaque	+ +	+ +	+	13
	+	+ +	+	
	+	+	0	
	+	+	0	
Hexabrix	+	+	+ +	9
	+	+	+	
	0	+	+	
	0	0	0	
Physiological saline	+	+	+	5
	+	+	0	
	0	0	0	
	0	0	0	
Control	0	+	+	3
	0	0	+	
	0	0	0	
	0	0	0	
Total	47	52	34	

0 no reaction; + mild reaction; + + moderate reaction; + + + severe reaction.
*Animals who died.
−Contrast agent not in pleura.

FIG. 1.

Radiographs taken immediately after introduction of contrast medium into pleura. (A) Postero-anterior and lateral radiographs of the chest showing Micropaque in the pleural spaces. (B) Hytrast visible only in the left pleural space with a left pneumothorax. (C) Hexabrix is seen to be mainly in the right pleural space with pneumothorax. A left pneumothorax is also visible.
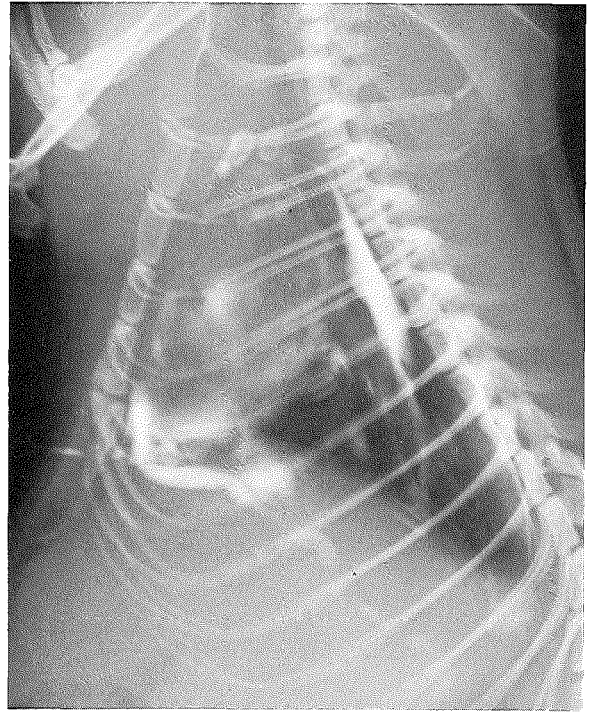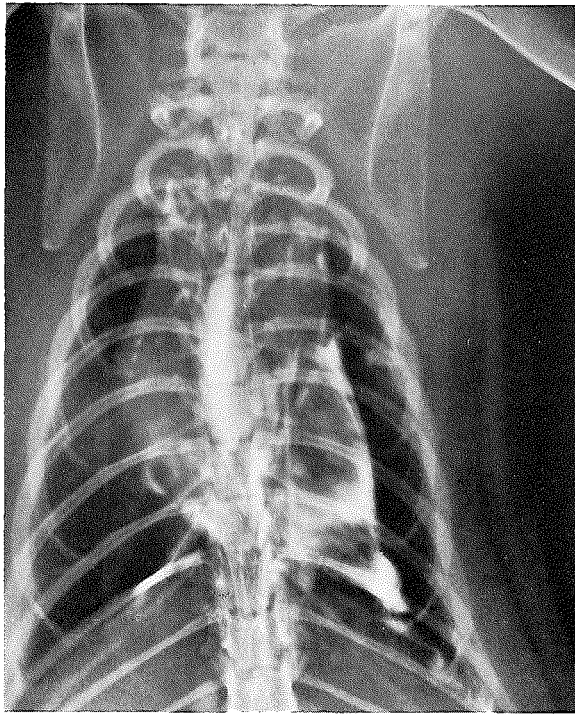
FIG. 2.

Postero-anterior and lateral radiographs taken 42 days after introduction of Micropaque (same rat as Fig. 1A). Very little change is in the quantity of contrast agent since the Day-1 radiographs (Fig. 1A).

Pathological findings

Gross examination. The gross abnormalities whenever present were always more marked on the side of injection (left side) than the right side of the chest. The chest wall wound appeared to be fully healed in the 8-day group.

Pure barium sulphate and Micropaque were seen as whitish plaques in places on the parietal pleural lining of the chest wall, on the pleural surface of the diaphragm and over the surface of the lung. The contrast agent appeared to collect mainly centrally in the loose connective tissue of the mediastinum, particularly in the infracardiac region. A slight to moderate pleural effusion, containing whitish contrast agent, was noted on Day 1 and the quantity of contrast agent on the left side was much more than on the right side of the chest. Adhesions were noted between the left lung and the mediastinum and to a lesser degree between the right lung and the mediastinum. These were most marked on Day 8, but also visible till Day 42. Areas of collapse/consolidation in the lungs were visible in some rats. Hytrast tended to clump, particularly in the mediastinal region, with moderate pleural effusion on Day 1: dark red areas were seen on the lung surfaces and in later stages some adhesions occurred between the lungs and the mediastinum. The

quantity of contrast agent and number of adhesions were, however, considerably reduced by Day 42. The Omnipaque, Gastrografin, Hexabrix, Dionosil and physiological saline groups showed no detectable pleural effusion or any sign of contrast agent at any stage on dissection. No collapse or consolidation of the lungs was noted on gross examination, nor any adhesions between the lung and the mediastinum. Adhesions were seen occasionally between lung and parietal pleura at the site of the injection in those animals where the lung was accidentally caught in the chest-wall stitches (nine animals).

Histological reaction

The histological changes were, in general, almost always most significant on the left side but less marked changes were often also found on the right side, particularly intrapulmonary abnormalities.

Pure barium sulphate. The histological reaction was more marked on the left side. At Day 1, deposits of contrast agent were seen in the parietal pleural lining of the thoracic wall, diaphragm and the mediastinal structures, and was mostly superficial and extracellular. The most abundant collection of contrast agent was seen in the infracardiac mediastinal fat and its pleural lining (Fig. 3). This was accompanied by a fibrinous,
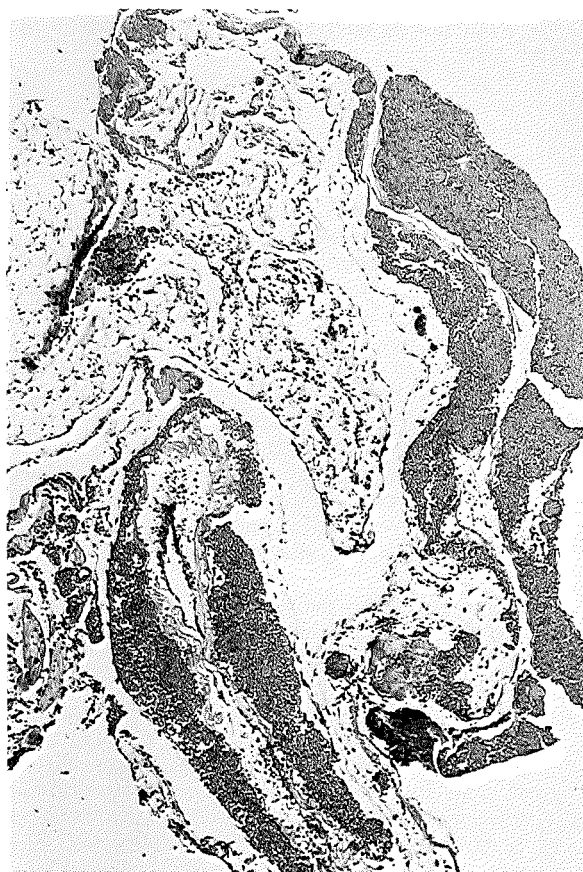
FIG. 3.

Histological section showing pure barium sulphate collections at Day 1 in the mediastinal infracardiac pleura and fatty tissue (haematoxylin and azophloxin, × 60).
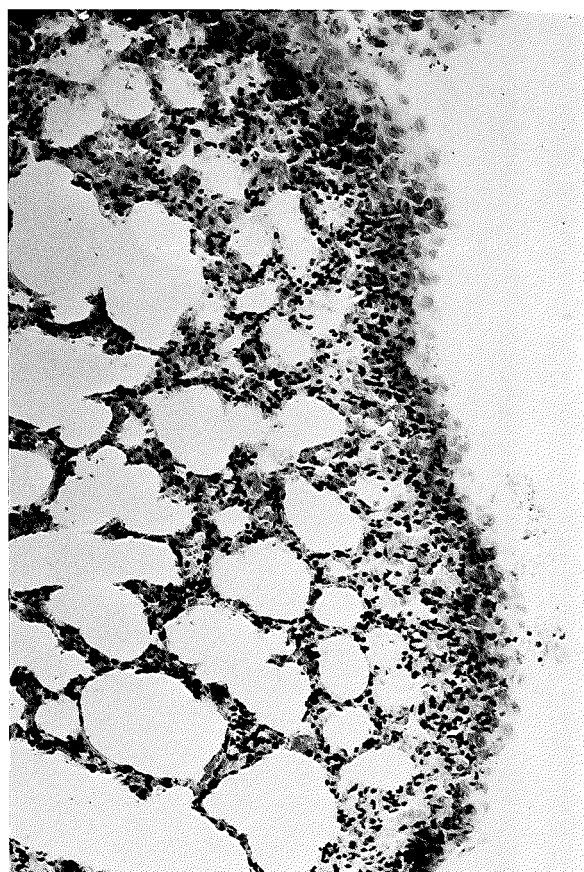

FIG. 4.

Histological section at Day 1 after Micropaque introduction, showing swelling and proliferation of visceral pleural mesothelial cells. No pulmonary parenchymal abnormalities are visible. (H & A, × 150).

histiocytic reaction with some polymorphonuclear cells. The visceral pleura covering the lung appeared swollen with small deposits scattered mainly over the surface and not intracellularly (Fig. 4).

On Day 8, the reaction of the parietal pleura was again most extensive in the mediastinal region, with much less change in the region of the diaphragm and chest wall. At this stage, extensive intracellular quantities of contrast agent were seen within the histiocytes with occasional multinucleated foreign-body giant cells. Similar but scattered reactions were also seen on the surface of the lung within the pleura.

At 42 days, extensive fibroblastic histiocytic infiltration was seen, with some lymphocytes and multinucleated giant cells in the parietal and visceral pleura (Fig. 5). The histiocytes were loaded with granular-looking contrast material. The reaction was most marked in the mediastinal fatty tissue and parietal pleura. In the lungs, small focal perivascular infiltrates were seen in most of the animals with lymphocytes,

histiocytes, polymorphs and eosinophils in places. This reaction was similar in both lungs, although the pleural reaction was always more marked on the side of injection of the contrast agent.

Micropaque. Histological reaction in the pleura caused by Micropaque was very similar to that by pure barium sulphate except that at 42 days the mediastinal lymph nodes also showed accumulation of some of the contrast agent within the histiocytes.

Hytrast. On Day 1, extensive deposition of contrast-agent crystals was seen in the pleura, particularly the mediastinum with local necrosis accompanied by fibrinous deposits and polymorph infiltration. Swelling of the mesothelial lining cells was noted with infiltration of histiocytes. The visceral pleura covering the lung showed a diffuse reaction with swelling of the subpleural mesothelial cells and polymorphs. The contrast agent was particularly concentrated in the mediastinal region of the pleura. Intrapulmonary foci of
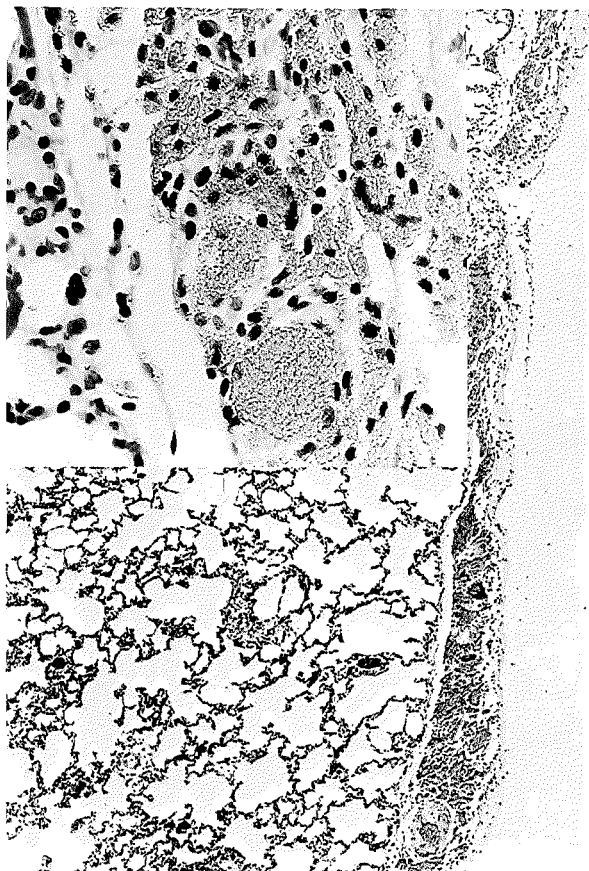
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FIG. 5.

Histological section at 42 days after pure barium sulphate injection showing visceral pleura with extensive granulomatous reaction with intracellular barium sulphate collections in histiocytes and multinucleated giant cells (H & A, × 60, inset H & A, × 380).

inflammatory reaction were also noted with small areas of collapse of the lung in places.

On Day 8, extensive fibrohistiocytic reaction with central necrosis was seen. Intracellular contrast-agent crystals were also seen in the histiocytic cells and multinucleated, foreign-body giant cells. The visceral pleura showed focal thickening with subpleural infiltration containing lymphocytes and eosinophils. Both lungs showed perivascular lymphocytic infiltrations with some eosinophils.

At Day 42, the pleural reaction was similar to that at Day 8 but less severe. The lymph nodes showed follicular lymphoid hyperplasia but no contrast agent was present.

Dionosil. On Day 1, swelling of the lining cells of the parietal pleura was seen with slight diffuse reaction with some histiocytes and polymorphs in places;

polymorphonuclear infiltration was also evident in the visceral pleura.

On Day 8, a fibrotic reaction was observed, with thickening of the parietal pleura and infiltration with histiocytes, polymorphs and eosinophils; on the visceral surface, there was focal proliferation of the subpleural tissue.

On Day 42, there was slight swelling of mesothelial cells of the parietal pleura with some fibrosis. Slight thickening of the visceral pleura was also seen in places, while subpleural and perivascular infiltrates with mononuclear cells were noted in both lungs at all stages, *i.e.* at 1 day, 8 days and 42 days.

Omnipaque. On Day 1, slight polymorphonuclear reaction with swelling of the mesothelium was noted in the parietal pleura. The visceral pleura showed some swelling of the cells with a slight inflammatory reaction. On Day 8, there was minimal reaction in the parietal pleura with slight subpleural and intrapulmonary infiltration with lymphocytes and histiocytes. On Day 42, a minimal reaction was seen similar to that of Day 8.

Hexabrix. On Day 1, swelling of the connective tissue was present in the mesothelium of the parietal pleura and a little fibrinous exudate was present in the visceral pleura of two animals. No intrapulmonary abnormality was seen. At Day 8, swelling of the parietal pleural mesothelium was seen with some plasma cells, histiocytes and eosinophils present. The visceral pleura showed some increase in the mesothelial stroma and there was slight intrapulmonary perivascular infiltration with polymorphs, histiocytes and lymphocytes. The lymph nodes showed follicular lymphoid hyperplasia. At Day 42 a similar reaction as at Day 8 was seen, except that there were no changes in the lymph nodes.

Gastrografin. On Day 1, minimal swelling of the parietal pleural mesothelium was seen with inflammatory infiltrates consisting of polymorphs and mononuclear cells. The visceral pleura showed some swelling of the mesothelial cells and, in the lungs, there were small subpleural and perivascular inflammatory infiltrates with polymorphs and mononuclear cells. On Day 8, a focal fibrotic reaction was noted in the parietal pleura with lymphocytes and polymorphs and swelling of the mesothelial lining cells. Swelling of cells was also seen in the visceral pleura. Intrapulmonary perivascular infiltrates with lymphocytes and histiocytes were also noted. At 42 days, a similar reaction to that on Day 8 was seen. The lymph nodes showed follicular lymphoid hyperplasia.

Physiological saline. On Days 1 and 8, slight infiltration and swelling of the mesothelial cells of the pleura was noted in some animals and there was slight perivascular intrapulmonary reaction with a few histiocytes and polymorphs. At the 42-day stage, except for slight infiltration of mesothelial lining of the pleura in one animal, no other abnormalities were seen.

Control group (anaesthetic only). Animals showed no abnormality on Day 1. Minimum perivascular

infiltrates with eosinophils, histiocytes and lymphocytes were seen in one animal in the 8-day group and in two animals in the 42-day group. In these animals the lymph nodes were rather large and showed nodular hyperplasia.

Table I summarises the histological reaction of the various contrast agents and physiological saline control group on the pleura of rats. The χ^2 test for K independent samples showed a highly significant difference between the various contrast agents ($p < 0.001$). The Hytrast, Micropaque and pure barium sulphate groups produced a highly significant reaction ($p < 0.001$) compared with the combined control group (physiological saline and anaesthetic-only control groups were joined together to form one group as they were not significantly different from each other). There was a significant difference between the combined control group and Omnipaque ($p < 0.01$). There was no significant difference between Hexabrix, Gastrografin, Dionosil and the combined control group.

DISCUSSION

This study forms a part of the experimental work carried out to find a safe and suitable contrast agent for use in the gastrointestinal tract in cases where leakage may be suspected outside the lumen of the gut, particularly post-operatively. The contrast agent in such cases may leak into the mediastinum, pleura or peritoneum, or enter the lungs either by aspiration or direct fistula formation. Ideally, the contrast agent should not produce any toxic effect should it enter any of these regions. The conventionally used water-soluble contrast agent Gastrografin has been shown to be unsafe if it enters the lungs and may even cause death (Ansell, 1968; Chiu & Gambach, 1974). Experimentally, too, Gastrografin has been found to be unsafe in the lungs (Frech et al, 1970; Ginai et al, 1984).

The tissue reaction to various contrast agents has already been evaluated experimentally in the lung (Ginai et al, 1984), mediastinum (Ginai et al, 1985) and peritoneum (Ginai, 1985). The present study shows the tissue reaction of the various contrast agents on the pleura of rats.

Micropaque, pure barium sulphate and Hytrast produced highly significant reactions ($p < 0.001$) in the pleura of rats compared with the control groups. Pure barium sulphate and Micropaque were both visible radiographically (although somewhat less dense) in the thorax up to the 42nd day, whereas only very slight Hytrast rests were visible on the Day-42 radiographs. Dionosil, Hexabrix, Omnipaque and Gastrografin were no longer visible on the Day-1 radiographs and appeared to be completely absorbed in the first 24 h.

The factors which lead to the absorption of the contrast agent in the pleural space and the exact route of removal can only be postulated on the basis of literature studies. Another puzzling question concerns presence of contrast agent in the right pleural space when it was carefully injected into the left pleural space.

The mechanics of the pleural space have been extensively studied and reviewed by Agostoni (1972). "The absorption of liquid from the pleural cavity may occur through the lymphatics and the blood, that of particles and large molecules only through the lymphatics" (Dybkowsky, 1866, cited in Agostoni, 1972). Courtice and Simmonds (1954) reviewed the lymphatic drainage from the pleural cavity and concluded that nearly all absorption takes place in the parietal pleura. The communications between the lymphatics and pleural cavity do not seem to be permanent but occur due to temporary dehiscence of adjoining mesothelial cells occurring when the pleura is stretched. The importance of respiratory movement for passage of liquid and particles through the mesothelial lining and subserous tissues into the lymphatics and for the propulsion of the lymph stream is paramount. The lymphatics therefore appear to be an important route for drainage of pleural liquid, proteins and particles. Courtice and Simmonds (1949) studied the absorption of fluids from the pleural cavities of rabbits and cats, in particular, the absorption rate of 0.9% sodium chloride solution and of plasma injected into the pleural cavities of normal rabbits. According to those authors, anaesthetics slow down the absorption, but in unanaesthetised animals both saline and plasma are absorbed at about the same rate. When they injected 6 ml/kg of fluid, practically all was absorbed in 24 h. The rate of absorption was greatly increased by increasing respiratory movements. They also pointed out the differences between animal experiments and man. "In experimental animals the pleural investment is thin; the visceral layer is supplied by pulmonary artery. The mediastinum is mobile and material injected into one pleural cavity is almost invariably removed later from both sides." The results in the present experimental study would also confirm their point of view, as the contrast agent injected in the left pleural space was almost always seen in the right pleural space on the radiographs. The absorption of water-soluble contrast agents was fairly rapid, possibly only a few hours since, at 24 h, no sign of any pleural effusion or contrast agent was seen. The mobility of the mediastinum and a possible connection between the two pleural spaces must account, in the case of certain animals, for the presence of contrast agent in both pleural cavities.

Black (1972) also reviewed the pleural space and pleural fluid and found that the pleural space normally contains a very small amount of fluid and that the lymphatics are located in the subendothelial layer of the parietal pleura. Anteriorly, the parietal pleura drains into the internal mammary system, while posteriorly the pleura is drained into the intercostal lymph nodes. Eventually, lymph enters the vascular system through the right lymphatic trunk or the thoracic duct. The lymphatics of the visceral pleura drain into the mediastinal lymphatic system and then into the venous system by right lymphatic trunk or thoracic duct. Particulate matter (such as graphite and colloid iron),

according to Courtice and Simmonds (1954), is absorbed mainly by the lower mediastinal pleura and costal parietal pleura in animals. Particulate matter is not absorbed by the visceral pleura. This fact is well demonstrated by the present experimental work, where pure barium sulphate and Micropaque were always found most abundantly in the inferior mediastinal pleura. The lower mediastinal pleura appears to the naked eye as a loose fatty tissue covered with pleural lining extending between the heart and diaphragm and anterior chest wall in the midline. The Micropaque series also showed filling of some of the mediastinal lymph nodes with contrast agent. This, however, was not found in the barium sulphate and Hytrast animals, which may be because not all of the mediastinal lymph nodes were included for histological section. It is also noteworthy that no absorption of the particulate contrast material is seen in the lungs and yet many lungs showed areas of patchy collapse and consolidation with all contrast agents. Although this may be due to intercurrent infection in some instances, the change is seen too frequently to be just a chance occurrence.

Another interesting observation is that the diaphragmatic lymphatics did not appear to fill with contrast agent. This is in contrast to the intraperitoneal injections (Ginai, 1985), where contrast agent filling of the diaphragmatic lymphatics and retrosternal lymphatics and lymph nodes was well defined in the case of pure barium sulphate, Micropaque and Hytrast. In the present series, no abdominal lymph nodes were seen to be filled with contrast agent. This difference in the peritoneal and pleural routes of absorption is also commented upon by Lemon and Higgins (1929). They point out the rarity with which pleural infections involve the peritoneum, whereas it is well known that pleural effusion may be associated with many abdominal pathological processes, such as Meig's syndrome, pancreatitis, peritoneal dialysis, and subphrenic abscess (Black, 1972).

In conclusion, the present study demonstrates that the water-soluble contrast agents Omnipaque, Gastrografin, Hexabrix and Dionosil cause the least reaction in the pleura, with Gastrografin and Hexabrix not being significantly different from the combined control group (saline/anaesthetic only). These two agents could be safely used, therefore, in cases where the possibility of leakage into the pleura may be suspected e.g. in the post-operative assessment of anastomotic upper gastrointestinal-tract surgery.

Previous experimental work on the lungs (Ginai et al, 1984) showed that Amipaque and Hexabrix were the least toxic contrast agents in the bronchi and lungs of rats, whereas Gastrografin caused significant reaction in these areas. Experimental work on the mediastinum (Ginai et al, 1985) demonstrated that Hexabrix and Gastrografin cause the least tissue reaction. Amipaque, Hexabrix and Gastrografin caused the least reaction in the peritoneum of rats (Ginai, 1985). In the light of these observations, it would appear that Gastrografin would not be suitable for use where there is risk of leakage directly into the lungs or aspiration into bronchi. This is because of a direct toxic effect on these tissues with the possibility of fatal reaction in patients if aspirated (Ansell, 1968; Chiu & Gambach, 1974). Amipaque is not ideal for practical use because of its high cost and its non-availability in a ready-to-use form.

In view of this, Hexabrix would be the contrast agent of choice in cases where leakage into the pleura, mediastinum or peritoneum may be suspected and aspiration may be an accompanying risk, and since starting its clinical use in our department, no untoward reactions have, so far, been recorded. A clinical study with Hexabrix is now being prepared.

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Intraperitoneal toxicity of hytrast:
an experimental study

ABSTRACT

The toxic effects of Hytrast were studied on the peritoneum of laboratory rats in order to define the lethal dose and possible causes of toxicity. The results show that Hytrast, due to its toxicity, should not be used in any clinical situation where gastrointestinal tract perforation or leakage is a possibility.

During the course of recent experimental work, carried out to find the most suitable contrast medium for use in the gastrointestinal tract in cases where leakage outside the gastrointestinal tract could be suspected (Ginai et al, 1984, 1985; Ginai 1985), we became aware of the toxic effects of Hytrast when injected into the peritoneum of rats. In our previous experimental study on the peritoneum (Ginai, 1985), all animals received 1.5 ml of one of the contrast media — Micropaque (Nicholas), pure barium sulphate, Dionosil (Glaxo), Hytrast (Guerbet), Gastrografin (Schering), Amipaque (Nyegaard) or Hexabrix (May & Baker) — intraperitoneally. It was planned to sacrifice the animals at intervals of 1 day, 2 days, 4 days, 8 days or 42 days after injection of contrast medium, but the Hytrast group reacted exceptionally badly in that all the animals died after about 48 h (Ginai, 1985). It is the purpose of this study to evaluate the toxic effects of Hytrast in the peritoneum of laboratory rats.

MATERIAL AND METHOD

Twenty male rats (Wistar strain, outbred stock, WU/Cpb (Zeist) weighing between 264 g and 295 g were used. The rats were divided into five groups of four rats each. Four of the groups received Hytrast (aqueous suspension of N-(propyl-2 : 3-diol)-3 : 5 diiodo-4-pyridone (NPP) and 3 : 5 diiodo-4-pyridone (DIP)) and Group 5 acted as a control (see below).

Group 1	1.5 ml	Hytrast
Group 2	0.75 ml	Hytrast
Group 3	0.375 ml	Hytrast
Group 4	0.19 ml	Hytrast
Group 5	1.5 ml	physiological saline

The rats were anaesthetised by ether inhalation. Hytrast or physiological saline was injected into the perioneal cavity with a blunt polyethylene catheter via a small midline abdominal incision. The incision was then closed with a surgical clip.

Frontal and lateral radiographs of the abdomen and thorax were taken immediately after injection of contrast medium and once again when any animal died or, otherwise, at sacrifice on the 42nd day. The following tissue biopsies were included at dissection:

(1) abdominal wall with the perioneal lining,
(2) diaphragm (both right and left side),
(3) liver,
(4) spleen,
(5) pancreas,
(6) kidney,
(7) greater omentum,
(8) mesentery,
(9) lymph nodes (thoracic and abdominal when possible),
(10) small bowel (at least two regions), and
(11) large bowel (at least two regions).

All the tissues removed were fixed in 10% buffered formalin for about 2 weeks before histological sections were prepared and stained with haematoxylin and azophloxin. The following grading system was used for the severity of histological reaction:

+ + + severe reaction,
+ + moderate reaction,
+ mild reaction,
± minimal reaction;
− no reaction.

RESULTS

All four animals in Group 1 (receiving 1.5 ml Hytrast) and two out of four animals in Group 2 (receiving 0.75 ml Hytrast) died. The four animals in Group 1 died within 48 h of administration of Hytrast. The two non-survivors in Group 2 died at 50 h and on the 10th day after injection of contrast medium. All the other animals survived and were sacrificed on the 42nd day.

The animals who died had appeared ill, their food and drink intake was only minimal and they had lost weight. The dissections on these animals were often carried out a few hours, sometimes up to 12 h, after their death. The animals who survived and were sacrificed on the 42nd day had put on a considerable amount of weight (about 200 g) and appeared generally well throughout the experimental procedure.

RADIOLOGICAL APPEARANCES

Group 1 (receiving 1.5 ml Hytrast) showed Hytrast spread around the intestines on the frontal and lateral radiographs taken immediately after intraperitoneal injection of contrast medium (Fig. 1). The radiographs of abdomen and thorax taken at about 48 h after contrast medium injection or after the death of these animals showed contrast medium to be flocculated and collected centrally and ventrally in the abdomen, and the bowel appeared denser, with contrast
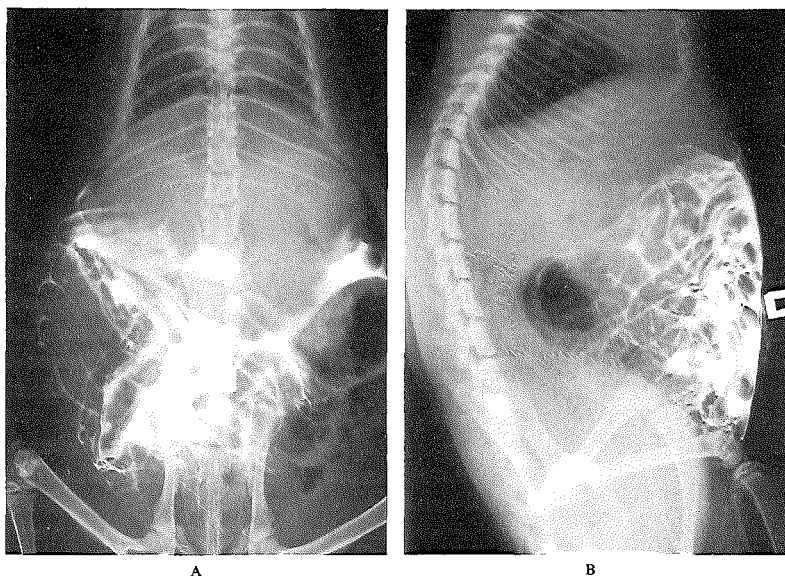
Fig. 1.
(A) Frontal and (B) lateral radiographs showing Hytrast (1,5 ml) in the abdomen of rat immediately after injection.

speckles (Fig. 2). The diaphragmatic lymphatic plexus, retrosternal lymph vessels and retrosternal superior mediastinal lymph nodes were seen to be filled with contrast medium on the radiographs (Fig. 2).

Group 2 (receiving 0.75 ml Hytrast). The quantity of Hytrast in the perioneal cavity was, naturally, less than (half) that in Group 1. Two animals died with similar appearances as Group 1. The two animals who survived were radiographed at 42 days, just before sacrifice, and showed small contrast rests in the abdomen.

Group 3 (receiving 0.375 ml Hytrast) and **Group 4**

(receiving 0.19 ml Hytrast). These groups had similar appearances on radiographs taken immediately after contrast medium injection, with the contrast medium spread around the intestines. The quantity of contrast medium in Group 3, as expected, appeared less than that in Group 2 and the quantity of contrast medium in Group 4 was less than in Group 3.

On the 42-day radiographs, minimal contrast rests were seen in the abdomen. There was no contrast medium seen filling the diaphragmatic lymphatics, retrosternal lymph vessels or lymph nodes.
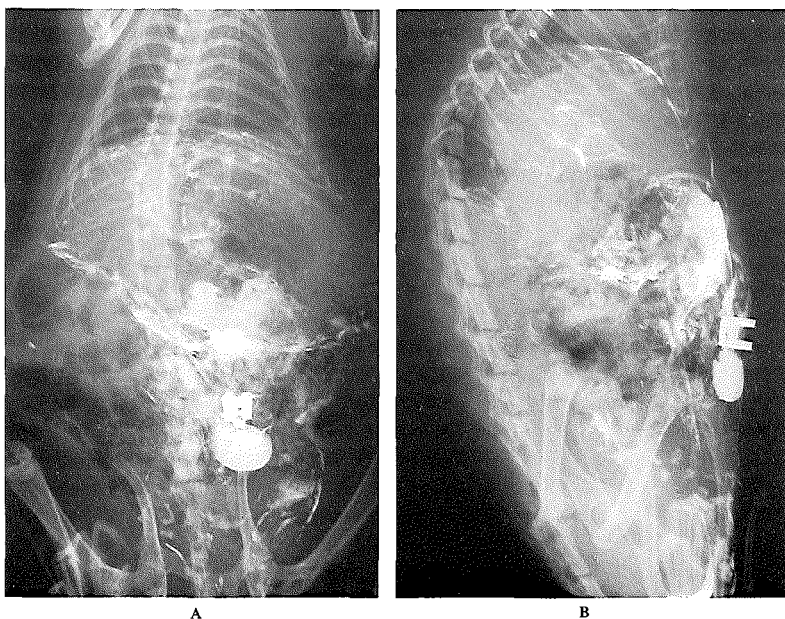
Fig. 2
Same rat as Fig. 1, 48 h after death. (A) Frontal and (B) lateral radiographs, showing flocculation of contrast medium and its collection more centrally and ventrally in the abdomen. Filling of the diaphragmatic and retrosternal lymphatics and mediastinal lymph nodes with contrast medium is visible.

Group 5 (receiving 1.5 ml physiological saline). This control group showed no abnormalities on the radiographs taken immediately after injection of contrast medium or 42 days after injection.

PATHOLOGICAL OBSERVATIONS

Gross appearances
Group 1. All four animals died about 48 h after injection. Dissection was often carried out several hours after death. A small amount of yellowish or reddish ascitic fluid was found in the abdomen. The contrast medium was seen as whitish plaques on the surface of the omentum, mesentery and abdominal wall and sometimes over the liver. The abdominal surface of the diaphragm showed filling of lymphatic plexuses on both sides. Contrast medium was also seen in the retrosternal lymphatics and lymph nodes.
Group 2. Two animals in this group died, one at 50 h and the other on the 10th day after injection. Slight ascites was seen in one and contrast medium was visible in the abdomen, though less than in Group 1. In the other rat, dying on the 10th day, practically no ascitic fluid was noted. Contrast medium was seen in the mediastinal lymph nodes in both of these rats. The remaining two rats were sacrificed on the 42nd day and showed only tiny contrast rests and some adhesions between the anterior abdominal wall and the small intestine. No ascites was noted. No filling of diaphragmatic lymphatics or retrosternal lymph vessels or lymph nodes was seen.
Group 3 and 4. These animals were sacrificed on the 42nd day and showed tiny contrast rests anteriorly, usually with some adhesions between the anterior abdominal wall and mesentery or small intestines. No ascites was seen. No filling of lymphatics in the diaphragm or restrosternal region was seen. Mediastinal lymph nodes were not filled with contrast medium.
Group 5. This control group showed no abnormalities on dissection at 42 days.

Histological appearances
Group 1. The abdominal wall and diaphragm showed extensive, acute inflammatory reaction with lymphocytic and histiocytic infiltration and deposits of contrast medium in some places. Necrotic areas were seen on the surface with extensive fibrinous exudate. Similar reaction could be seen in the capsule of the liver. The liver parenchyma was normal. The kidney showed no abnormality. The spleen showed decrease of lymphocytes in the parenchyma. The omentum and peripancreatic fatty tissue showed deposits of contrast medium with a surrounding inflammatory infiltrate (Fig. 3). Contrast medium could sometimes be seen in the mesentery adjacent to the bowel. Transmural segmental necrosis was seen in the large and small bowels and there were also some areas of superficial mucosal and submucosal necrosis. Contrast medium was not visible in the mucosal, submucosal or muscular layers of the bowel. The mediastinal lymph nodes showed necrotising lymphadenitis.
Group 2. The two animals who died showed deposition of contrast medium and inflammatory reaction with histiocytic infiltration in the abdominal wall, diaphragm, omentum and

Fig. 3.
Histological section showing Hytrast (H) deposits with inflammatory reaction in the peripancreatic fat (P). Haematoxylin and azophloxin, x 40.

mesentery. Areas of necrosis were also seen in the peripancreatic fatty tissue. In the lymph nodes a sinus histiocytosis was noted. The small and large bowels showed some areas of necrosis. The two survivors showed no specific abnormalities except small contrast medium deposits in the omentum, with minimal areas of inflammatory cell infiltration.
Group 3. Small deposits of contrast medium were seen in the omentum and mesentery. Some small areas of necrosis were seen in the mucosa of the small bowel and focally in the muscle layer in one of the animals.
Group 4. Fibrosing, chronic inflammatory reaction was seen in the abdominal-wall muscles in one of the animals (probably the site of abdominal incision). Tiny rests of contrast medium were seen in the mesentery and around the liver capsule. In one instance chronic inflammatory reaction was seen in the pancreatic tissue. The bowel showed no abnormality.
Group 5. This control group showed minimal inflammatory infiltrate in the peripancreatic fatty tissue. In one animal, the small bowel showed partial necrosis in places in the superficial layers of mucosa and submucosa.
Table I summarises the tissue reaction with various doses of Hytrast in the perioneum of rats.

DISCUSSION
The most severe tissue reactions were seen in Group 1 (receiving 1.5 ml Hytrast), in which all the animals died. Two of the animals in Group 2 (receiving 0.75 ml Hytrast) also died, and these showed moderately severe reaction. All the other animals (10 with Hytrast and four controls) survived and were in good condition when sacrificed on the 42nd day. These animals showed mild to minimal or no tissue reaction (Table 1).
It would, therefore, appear from this study that 1.5 ml of Hytrast intraperitoneally is an absolutely lethal dose for rats weighing about 280 g and that half the dose (0.75 ml of Hytrast) intraperitoneally caused half the animals to die.

TABLE I

Histological reaction in the peritoneal tissues of 16 rats receiving Hytrast and controls

Animals Group				
1 (1.5 ml Hytrast)	2 (0,75 ml Hytrast)	3 (0,375 ml Hytrast)	4 (0,19 ml Hytrast)	5 (1,5 ml physiological saline)
1	+++°	++°	+	+	±
2	+++°	++°	+	+	±
3	+++°	+	±	±	±
4	+++°	+	±	±	−

° Animals who died; +++ severe reaction; ++ moderate reaction; + mild reaction; ± minimal reaction; − no reaction.

Further reduction of the Hytrast dose, to a quarter (0.375 ml) and an eighth (0.19 ml) of the original dosage, lead to no deaths.

The full dose of Hytrast used in rats, i.e. 1.5 ml, is equivalent to about 375 ml in a 70 kg man, an amount of contrast medium which could possibly enter the peritoneum in a clinical situation of bowel perforation.

From the general clinical, gross pathological and histological appearances seen in the animals who died, the most likely cause of death appears to be a severe exudative, necrotising perionitis in all tissues of the peritoneum with which Hytrast comes in contact. The liver parenchyma, pancreas and kidney showed no abnormalities. The spleen showed a decrease in lymphocytes. The lymph nodes showed deposition of contrast medium in Group 1 and half of the rats in Group 2, with some necrosis and sinus histiocytosis. This was also noted in the previous experimental work with various contrast media in the peritoneum (Ginai, 1985) and does not appear to be directly related to the death of these animals.

The intestines showed partial or complete intramural necrosis in places. These appearances could suggest ischaemic changes possibly resulting from shock arising from acute peritonitis. It is, however, not possible to confirm this hypothesis or to define any direct relationship between bowel necrosis and death of the animals, as some necrosis was also seen in the animals who survived and even in the control group. Some autolysis or technical factors may also have played a role in these appearances of the bowel.

Hytrast was introduced as a bronchographic contrast medium in 1962. It is a neutral suspension of crystals of N-(propyl-2 : 3-diol)-3 : 5 diiodo-4-pyridone and 3 : 5 diiodo-4-pyridone in a hypertonic aqueous solution of sodium carboxymethyl cellulose (Morley, 1969). The viscosity varies from 6 poises (French preparation) to 2.4 poises (American preparation) at 37°C depending on the quantity of methyl cellulose used in its preparation (Grainger et al, 1970). Hytrast can produce excellent-quality bronchograms but is known to have caused significant reactions in the lungs both in humans and in animals (Greenberg, 1964; Ginai et al, 1984).

Thirty-eight cases of severe reactions following bronchography with Hytrast (including one death) were reported by Agee and Shires (1965). Hytrast also produced the severest reaction in the mediastinum compared with all other contrast media used in the experimental work done on the mediastinum of rats (Ginai et al, 1985). Considering the severe toxicity of Hytrast in the peritoneum (Ginai, 1985) of rats and the very severe toxic reactions in the mediastinum, lungs and pleura of rats (Ginai et al, 1984, 1985; Ginai, 1986), this contrast medium should not be used in the gastroinestinal tract in cases where leakage in any of the above-mentioned regions is a possibility, for example, in post-operative patients with gastrointestinal-tract anastomosis or any other cases where gastrointestinal-tract perforation is suspected.

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Clinical use of Hexabrix for radiological evaluation of leakage from the upper Gastrointestinal tract based on experimental study

ABSTRACT

The clinical use of Hexabrix (May and Baker) was started about 3.5 years ago for the radiological evaluation of patients in whom the possibility of leakage of contrast medium outside the upper gastrointestinal tract, particularly the oesophagus, was anticipated. The majority (>70%) of the patients were in their early postoperative period. No adverse reactions because of the use of Hexabrix were encountered.

Which contrast medium to use in cases of suspected leakage from the gastrointestinal tract is a question which continues to be asked because of the lack of an ideal medium for radiological examination in such clinical situations as perforations of the upper gastrointestinal tract (GIT), in particular the oesophagus. This question is relevant, not only to spontaneous or iatrogenic perforations of the oesophagus, but, in recent years, to the postoperative radiological assessment often required following advanced oesophageal surgery.

The choice of contrast medium in such cases poses several important questions as to its safety and suitability. Apart from its suitable imaging properties, the contrast medium ideally should not cause any damage to tissues with which it comes in contact, nor produce immediate, early or late toxic effects.

The tissue reaction to several contrast media was experimentally evaluated in the rat bronchi and lungs (Ginai et al, 1984), mediastinum (Ginai et al, 1985), peritoneum (Ginai, 1985) and pleura (Ginai, 1986). The results of these studies showed that the low-osmolality contrast media Hexabrix, Amipaque (Nycomed UK Ltd) and, later, Omnipaque (Nycomed UK Ltd) caused the least reaction when all the various tissues were taken into account. The use of Hexabrix was started clinically in November 1982. To date, over 400 upper GIT examinations with Hexabrix have been carried out and no untoward reactions have been encountered. This article deals with the experiences of the use of Hexabrix in the upper GIT in the first 2-year period, November 1982-November 1984.

PATIENTS AND METHOD

Records were kept of the contrast agent used for all examinations of the upper GIT performed in the 2-year period starting November 1982. One hundred and sixty-seven patients had a Hexabrix swallow examination. The patients (113 men and 54 women), aged 15-95 years, for whom the radiographs and/or video recordings of Hexabrix examinations were available were reviewed. The following data were used for analysis: Age and sex of the patient, clinical diagnosis and (if postoperative) the nature of surgery, indication for Hexabrix swallow, diagnostic quality and density of contrast on the radiographs and any recorded side-effects ascribable to the contrast medium.

Method of examination

The patients were examined in the horizontal, semi-erect and/or erect positions, depending on their physical condition and indications. Effort was made to obtain a minimum of two right-angle views using as small an amount of contrast medium as possible. Hexabrix 320 mg I/ml was used in all oesoghageal examinations in the series. The amount of contrast medium used usually varied between 20 ml and 50 ml but occasionally up to 100 ml was used. If severe aspiration was noted with the first swallow (which in cases of clinical suspicion was made in the lateral position for early recognition) the examination was either stopped if the information gained was adequate, or repeated with a second swallow for further information only if absolutely essentail. Large quantities of contrast medium were never used in such cases and a video recording was employed in order not to miss any useful information in difficult situations. In postoperative cases, the Hexabrix swallow was performed at about the eighth postoperative day, and if an anastomotic leakage was found, a repeat examination was carried out after a further 4-7 days, initially with Hexabrix.

Plain radiographs ware often taken before the contrast medium was used and late radiographs were obtained 15 min-60 min after Hexabrix swallow in case of a doubtful leakage. The diagnosis is such cases was almost always made on a combination of fluoroscopy (and in some cases video recordings) and radiographs.

The indications for the use of Hexabrix as the initial contrast medium in the present series were as follows.

(1) Postoperative (around eighth postoperative day) after oesophageal (75 patients) or pharyngeal and laryngeal surgery (40 patients) (total 115 patients).
(2) After certain endoscopic procedures where leakage could be suspected, including laser myotomy for Zenker's diverticulum (five patients), prosthetic tube insertion as palliative measure in patients with inoperable oesophageal carcinoma (14 patients), removal of foreign body (two patients) and dilatation of stricture (one patient) (total 22 patients).

(3) Miscellaneous indications including iatrogenic perforations of the oesophagus, e.g. foreign body in oesophagus or after lye (caustic soda) ingestion and in patients with very narrow strictures of the oesophagus in whom severe aspiration could be anticipated as also with certain abnormalities of the swallowing mechanism (total 30 patients).

RESULTS

No adverse reactions were encountered because of the use of Hexabrix 320 in the upper GIT when used in the quantities and method described. The significant abnormal findings are listed as: leakages into the mediastinum or soft tissues, 17; pulmonary aspiration, 25; oesophago-bronchio-tracheo-pleural fistulae, eight; filling of abscess cavity in soft tissue of the neck or lung apex, four.

The radiographs were judged on the basis of the contrast density and diagnostic quality and varied from "excellent" to "acceptable" for diagnosis in 128 patients (Figs 1, 2, 3, 4). Nineteen patients had only a video recording of the Hexabrix swallow, and were all "good" to "diagnostic" in quality. Twenty patients had "barely-diagnostic" to "poor" quality radiographs, but fluoroscopy had helped to reach the correct diagnostic conclusion in most of these cases. However, in one patient with a Celestin prosthetic tube, an oesophago-bronchial fistula was missed and was not seen even in retrospect on the radiographs. In another postoperative patient with intrathoracic oesophago-gastric anastomosis, a leakage of contrast medium was not demonstrated, but was later shown as a large oesophago-

pleural leak on CT. Apart from these two patients, no false negatives were noted. Many of the mediastinal leakages in the patients with postoperative anastomoses were tiny (pocketed) and most of these were not present on repeat examination. Only a minority of the patients required repeat examinations but the patient with the oesophago-pleural fistula had to be examined several times, as the fistula did not appear to close even after surgery (Fig. 5).

DISCUSSION

The radiologist has a vital role to play in the important diagnosis of perforation of the oesophagus and its localisation. The most important factor in reducing morbidity and mortality in oesophageal rupture is early diagnosis and immediate surgical intervention, a view supported by a large number of publications in the literature (Vessal et al, 1975). Fluoroscopy using contrast medium is of great assistance in providing the necessary information and an ideal contrast medium for use in such cases of leakage should have the following qualities.

(1) It should have adequate radio-opacity.
(2) If aspirated into the lungs in small quantities, it should not cause any immediate or long-term toxic reactions.
(3) If leakage occurs into the mediastinum or soft tissues (e.g. of the neck), it should not cause any immediate or long-term toxic effects.
(4) Should it enter the pleural or peritoneal cavity, it should, again, not cause any significant short- or long-term reactions.
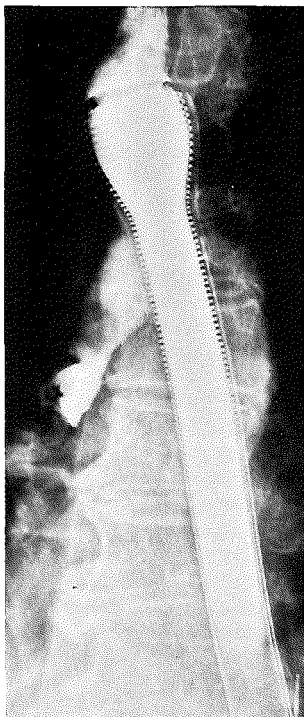(5) It should be palatable for the patient when used orally.

Fig. 1.
Hexabrix swallow showing perforation, with contrast medium in the mediastinum on the right side of a prosthetic (Celestin) oesophageal tube inserted endoscopically as palliative therapy for inoperable oesophageal carcinoma.
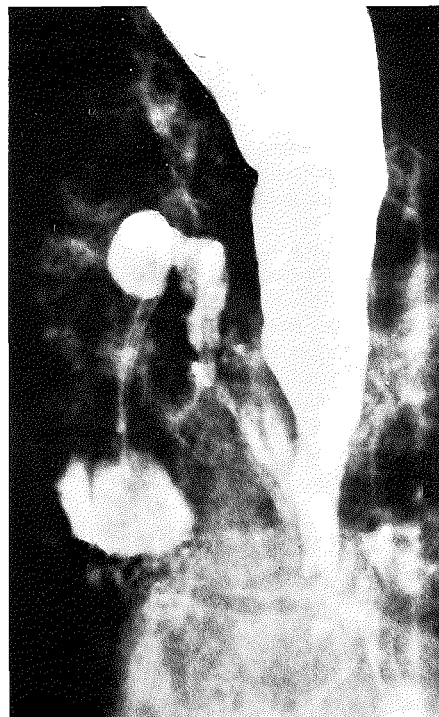
Fig. 2.
A 38-year-old man with a perforation of the oesophagus at the site of an old caustic-soda stricture. The perforation was accidently induced by the patient while pushing the food through the strictured oesophagus with a metallic wire (a habit he had acquired a long time ago to relieve food obstrucion!). Hexabrix swallow shows leakage of contrast medium into the mediastinum to the right at the site of perforation with a narrow stricture distally and a rather wide obstructed proximal oesophagus.
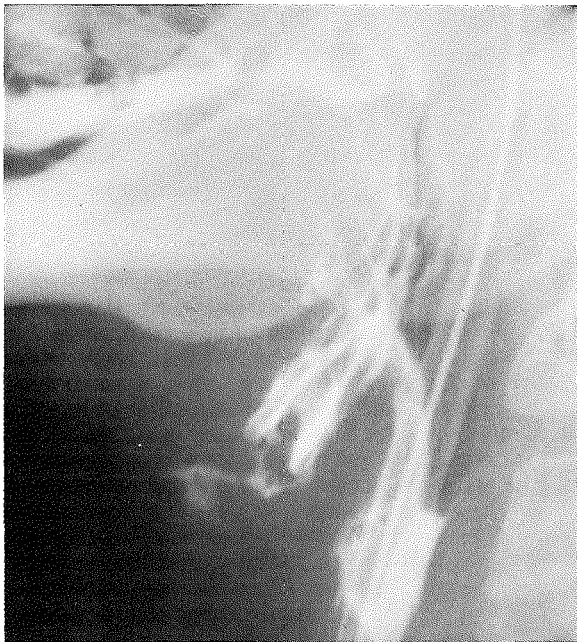
Fig. 3.
A small leakage is shown on Hexabrix swallow in the soft tissues of the neck, below the mandible in a patient who had had a recent total larynx extirpation.

Because the literature contained no complete study on the tissue reactions of the available contrast media in these various sites, we carried out an experimental study on rats (Ginai et al, 1984; Ginai, 1985; Ginai et al, 1985; Ginai,1986).

Barium sulphate is an ideal contrast medium for routine visualisation of the intact GIT, owing to its superior radiographic density and chemical inertness. Free barium sulphate in the peritoneal cavity, however, causes an immediate inflammatory reaction and subsequently leads to the formation of granulomas. Within a few hours, free intraperinoneal barium sulphate is entrapped in, and cannot be removed from, the peritoneum or serosal surfaces (Zheutlin et al, 1952). Pure barium sulphate, according to some authors (Revill, 1971), causes less reaction because of lack of coating agents and additives. It appeared, however,
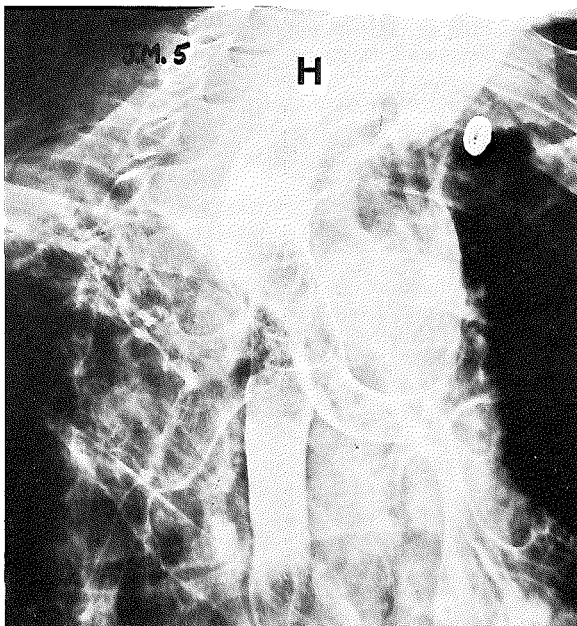
Fig. 4.
Hexabrix swallow showing severe aspiration in a 78-year-old patient with an abnormal swallowing mechanism secondary to chronic subdural haematoma.
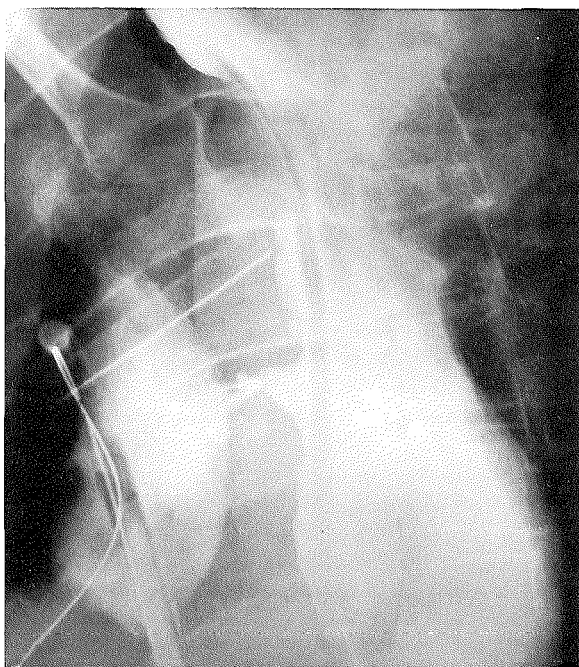
to cause a similar tissue reaction as commercial barium sulphate in the experimental work carried out on the peritoneum of rats (Ginai, 1985). Encapsulation of barium sulphate in scar tissue, fibrotic adhesions and granuloma formation was clearly seen in the animal studies and has been described in the literature as the cause of eventual intestinal obstruction and mortality (Zheutlin et al, 1952) or urethral obstruction (Herrington, 1966), even long after the initial exposure.

Gastrografin (Schering AG) appears to have several disavantages due to in its high osmolality ($\pm$ 1900 mosmols/kg water), the most serious being the possibility of fatal pulmonary oedema if aspirated into the lungs (Ansell, 1968; Chiu & Gambach, 1974). Experimentally too, Gastrografin has been known to cause serious or significant reaction in the rat lung (Frech et al, 1970; Ginai et al, 1984).

Hexabrix is a water-soluble contrast medium which is a 2:1 mixture of meglumine and sodium salts of ioxaglic acid, a monoacid dimer of two benzine rings with six iodine atoms attached. At a concentration of 320 mg I/ml, Hexabrix has an osmolality approximately twice that of blood (Grainger, 1979). The non-ionic contrast media Amipaque and Omnipaque also have an osmolality about twice that of plasma at concentrations of 300 mgI/ml. Because of their low osmolality, Hexabrix and the non-ionic media Amipaque and Omnipaque and possibly also other, newer lower-osmolality contrast media (e.g. Niopam, Bracco) would appear to be suitable for use in any circumstances where leakage from the GIT is suspected and aspiration is an accompanying risk.

CONCLUSION

On the basis of the experimental study on the tissue reaction of various contrast media on lungs, bronchi, mediastinum, pleura and peritoneum of rats, Hexabrix and Amipaque appeared to be the safest media, taking all these tissues into account. The use of Hexabrix, because of its availability as a ready-to-administer solution began about 3½ years ago for the evaluation of patients with the possibility of leakage outside the upper GIT. The use of Hexabrix in the first 2-year period has been evaluated and has shown no adverse effects attributable to the contrast medium with the quantities and the technique of the examination employed. Hexabrix, or possibly another low-osmolality contrast medium such as the non-ionic Omnipaque or Amipaque, should therefore be the contrast media of choice for initial radiological evaluation in cases of leakage from the upper GIT. If such initial study demonstrates no evidence of leakage, the use of a commercial barium-sulphate suspension for further examination would then be justified.

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General discussion and conclusion

The correct choice of contrast medium for the evaluation of leakage from the GIT is important in order to avoid further complications due to the use of contrast medium itself. The CM should cause no short or long term local or general reactions in the lungs, mediastinum, peritoneum or pleura. Leakage of barium sulphate into the peritoneal cavity is known to be a catastrophic event as this CM is not absorbable or easily removable (eg., at surgery) and its presence is associated with inflammatory granulomatous and fibrous reaction. This can later lead to adhesions and bowel obstruction, which may be fatal. The use of barium sulphate in any patient with a possible abdominal perforation is therefore contraindicated.

Revill (1971) has suggested the role of additives in "commercial" barium sulphate in giving the granulomatous reaction and formation of adhesions in the peritoneum, however the present experimental study has shown no significant difference in the severity of the histological reaction caused by "pure" and "commercial" barium sulphate in the peritoneum, lungs, pleura or mediastinum. Inflammatory reaction and enhanced morbidity and even mortality has also been described due to the presence of barium sulphate in the lungs both in animals and in human beings (McAlister, et al., 1981; Ratcliffe, 1983). Barium sulphate when aspirated may block the bronchi in addition to causing chronic granulomatous reaction. This effect of barium sulphate can be particularly hazardous in babies and young children and also adults with poor respiratory reserve. The present experimental study has shown a highly significant reaction due to barium sulphate in the lung. Severe reaction with granuloma formation and fibrosis was also seen in the mediastinal tissues and the pleural lining of the rat lung with barium sulphate. The use of barium sulphate in any suspected GIT leakage should be contra-indicated.

Hytrast and Dionosil are two iodine containing contrast media routinely used for bronchography which were also evaluated in this experimental study. Their effects in the mediastinum, pleura and peritoneum were not known and no literature could be found to this regard. Hytrast proved, in the present experiments, to be fatal for the rats when given intraperitoneally and also gave highly significant necrotising inflammatory reactions in the lung, media-stinum and pleura. These findings make Hytrast quite unsuitable for use in any suspected GIT perforation. In our opinion which is formed on the basis of the experimental study and study of the literature Hytrast is too toxic for use even as a bronchographic contrast medium.

Dionosil also gave an insignificant reaction in the rat lung, which was approximately half the intensity of the tissue reaction caused by Hytrast. In the mediastinum and perito-neum it gave a significant histological reaction, but the reaction of Dionosil was mild in the pleura. Dionosil therefore also appears not to be suitable for use in GIT leakage and moreover, its higher viscosity may be a dis-advantage in demonstration of tiny leaks.

Gastrografin, a conventional water-soluble contrast medium has been widely used for evaluation of leakage from the GIT. Due to its hyperosmolality ($\pm$ 1900 m.osmols/Kg) compared to plasma and other body fluids (300 m.osmols/Kg) it is associated with a risk of serious reactions particularly on entering the lungs either by fistula or by aspiration.

Gastrografin has been associated with several fatalities in the past (Ansell, 1968, Chiu and Gambach, 1974; and personal communications) due to production of pulmonary oedema resulting from its high osmolality. The present experimental work has also demonstrated a significant reaction caused by Gastrografin in the lung. The other tissues i.e., mediastinum, pleura and peritoneum do not show as significant reaction by Gastrografin as the lungs. Since reaction in the bronchi and lungs carries with it a serious consequence of possible fatality, the use of Gastrografin as a CM should certainly be discontinued in the upper GIT leakage. Its use in the GIT of babies or small children could be hazardous particulary when they are dehydrated.

A high osmolality appears to be the major factor in causing the adverse reactions associated with conventional iodine containing water-soluble contrast media such as Gastrografin in the GIT. Amnipaque, Omnipaque and Hexabrix showed very mild reactions in all the tissues examined ie., lungs, mediastinum, peritoneum and pleura. The histological reaction caused by these contrast media in the lung was actually not significantly different from that of the control groups which received physiological saline or only the anaesthetic. Amnipaque, Omnipaque and Hexabrix have a lower osmolality, which is about ⅓rd compared to the conventional contrast media such as Gastrografin at a similar iodine concentration.

In conclusion the lower osmolality contrast media Hexabrix, Amipaque and Omnipaque are safer than all

other CM examined in the experimental study, for the evaluation of leakage from the gastrointestinal tract particulary in patients in whom possibility of leakage or aspirations to the lungs exists. On this basis clinical use of Hexabrix in the UGIT was started $\pm$ 4 years ago and has so far shown no untoward effects due to the use of this contrast medium.

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Summary

The aim of this investigation has been to find a safe and suitable contrast medium for radiological evaluation of the gastrointestinal tract in cases where leakage outside the GIT can be suspected. Leakage outside the gastro-intestinal tract lumen can occur in many ways eg., spontaneously, due to a disease process, iatrogenically or postoperatively at the site of anastomosis. The contrast medium used for the radiological evaluation of such patients could leak outside the lumen of the GIT and enter the mediastinum, pleura, peritoneum or bronchi and lungs. It is therefore essential to use a contrast medium, which would be safe should it leak into one or more of the regions mentioned. An experimental study was carried out to evaluate the reactions of various available CM in the bronchi and lungs, mediastinum, pleura and peritoneum of rats. The CM evaluated in the experimental study were, pure barium sulphate (without any additives), commercial barium sulphate (Micropaque, with additives), Dionosil, Hytrast, Gastrografin, Amipaque (in pleura Omnipaque) and Hexabrix.

The results of all the experiments taken together show that lower osmolality contrast media Hexabrix, Amipaque and Omnipaque are safer than all other CM examined experimentally, for radiological evaluation of leakage from the GIT. The clinical use of Hexabrix was started $\pm$ 4 years ago for the examination of suspected UGIT leakage and has, so far, shown no untoward or negative effects.

The aim and introduction in Chapter 1 are followed by various aspects of the contrast media in chapters 2 and 3. Chapter 4 deals with the aetiology of leakage, experimental investigation, clinical experience and method of radiological evaluation of gastrointestinal tract leakage. Chapters 5, 6, 7, 8 and 9 deal comprehensively with the experimental study. The clinical use of Hexabrix in the UGIT is described in chapter 10. The general discussion and conclusions are given in chapter 11.

Samenvatting

Het doel van dit onderzoek was het vinden van een veilig contrastmiddel voor gebruik in de tractus digestivus in geval van lekkage.

Lekkage buiten het lumen van de tractus digestivus kan op vele manieren voorkomen: spontaan, door afwijkingen in de darm zelf, iatrogeen of postoperatief op een anastomoseplaats. Het contrastmiddel, dat voor het onderzoek wordt gebruikt, kan in geval van lekkage terecht komen in het mediastinum, de peritoneale of pleurale holte, in de bronchi of longen. Daarom is het belangrijk een contrastmiddel te gebruiken, dat zo weinig mogelijk toxische reaktie in de weefsels veroorzaakt.

Een experimenteel onderzoek bij ratten vond plaats om de weefsel reakties van bronchi, longen, mediastinum, pleura en peritoneum na te gaan op de verschillende beschikbare contrastmiddelen.

De contrastmiddelen, die voor dit onderzoek werden gebruikt, waren puur barium sulfaat (zonder toevoeging), commercieel barium sulfaat (met toevoegingen; Micropaque), Dionosil, Hytrast, Gastrografin, Amipaque, Omnipaque en Hexabrix.

Dit onderzoek heeft aangetoond, dat contrastmiddelen met een lage osmolaliteit, zoals Hexabrix, Amipaque en Omnipaque, veiliger zijn dan de overige onderzochte contrastmiddelen bij radiologische evaluatie van lekkage vanuit de tractus digestivus, vooral bij patienten met de mogelijkheid van aspiratie of lekkage naar het longweefsel.

Op grond van de gegevens uit het experimentele onderzoek werd ongeveer 4 jaar geleden aangevangen met het toedienen van Hexabrix voor radiologisch onderzoek bij klinische patienten. Evaluatie van deze onderzoekingen kon tot nu toe geen bijwerkingen als gevolg van het gebruik van dit contrastmiddel aantonen.

In hoofdstuk 1 worden de doelstelling en introduktie aangegeven, gevolgd door hoofdstuk 2 en 3, waarin naast een historisch overzicht, sommige aspekten van de verschillende contrastmiddelen worden besproken.

Hoofdstuk 4 gaat over de etiologie van lekkage, de opzet van het experimentele onderzoek, klinische toepassingen en de methode van gebruik van contrastmiddel bij radiologische evaluatie van lekkage (en perforatie) vanuit de tractus digestivus.

De hoofdstukken 5, 6, 7, 8 en 9 handelen over de experimentele onderzoekingen.

Hoofdstuk 10 omvat het klinisch gebruik van Hexabrix voor radiologisch onderzoek van het bovenste deel van de tractus digestivus. Daarna volgen de algemene discussie en conclusies in hoofdstuk 11.

Acknoledgements

Curriculum Vitae

Abida Zahra Ginai-Karamat, was born on the 21st of June 1943 in Lahore, Pakistan. She passed the high school examination in 1958 and the premedical examination in 1960. A national Talent Medal was awarded to her, for securing the highest marks in Lahore division in the high school examination. Her medical studies started in 1960, at the King Edward Medical College, Lahore. In 1962, the degree of B.Sc., was taken. The medical graduation, M.B., B.S., degree, was taken in May 1965. She was awarded the Neil Memorial medal for standing first in Surgery and was also awarded the Dr Bishan Das Medal for second position in the university in the M.B., B.S., examination.

From September 1965 to February 1966, she worked as a house officer in Internal Medicine at the University Mayo Hospital, Lahore. Between March 1966 and February 1967, she worked as a medical officer at the Civil Hospital, Benghazi. She worked as a Senior house officer in Obstetrics and Gynaecology from August 1968 to January 1971 at the North Cambridgeshire and Bowthorpe Hospitals, Cambridgehire, England. The D.Obst., R.C.O.G., (London) was obtained in 1969.

She worked as a Registrar in Radiology from 1971 to 1974 at the Northwick Park Hospital and Postgraduate Research Centre, Harrow, London.

The D.M.R.D. (London) was obtained in October 1973. She was appointed a Senior Registrar in Radiology from June 1974 to June 1975 at the Northwick Park Hospital, Harrow, London. From June 1975 to March 1978 she worked as a radiologist on the Staff of the Havenziekenhuis in Rotterdam. She joined the Department of Diagnostic Radiology (Head Professor K. Hoornstra), University Hospital Dijkzigt, Rotterdam, as a staff-member in June 1978 and is still in post.