THE PANCREATIC SCAN

An Assessment of the Value of the ^{75}Se – Selenoamino Acids as Pancreatic Scanning Agents and Their Use in the Diagnosis of Pancreatic Disease.

A Thesis submitted for the
degree of
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to the
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by

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This thesis is dedicated to my Teachers
and above all, my Parents.

SUMMARY

This thesis represents an appraisal of the ^{75}Se labelled selenoamino acids, ^{75}Se - selenomethionine and ^{75}Se - selenocystine, as pancreatic scanning agents and their value in the diagnosis of pancreatic disease.

The normal and abnormal ^{75}Se - selenomethionine pancreatic scan was assessed in a study of 200 patients. The state of the pancreas was assessed clinically and by a variety of biochemical and radiological procedures. The tests performed varied from patient to patient. However, direct visualisation of the pancreas was considered the most certain way of confirming the scan observations and this was done in 104 (52%) patients at laparotomy or autopsy. The features of the normal and abnormal scan are presented. In general a wide variety of disease processes associated with a reduction of pancreatic exocrine function are likely to diminish uptake of ^{75}Se - selenomethionine by the pancreas. The majority of scans do not offer a definitive pathological diagnosis on the features of the scan alone. In a controlled study of the final 40 consecutive patients scanned, it was found that the diagnostic accuracy of pancreatic scan reporting may be greater than 90% in determining whether the pancreas is "normal" or "abnormal". The criteria for this assessment were determined by prior study of the first 160 patients in the series.

Observations based on whole-body counting, organ distribution studies and abdominal scans in rabbits and in human subjects injected with ^{75}Se - selenocystine, showed that a large fraction of the injected isotope is rapidly excreted by the kidneys. This results in a strong renogram effect on the scan and because the tail of the pancreas consistently overlaps the upper pole of the left kidney, renal uptake of the isotope will tend to mask changes in the overlying tail of pancreas. For this reason it is unlikely that ^{75}Se - selenocystine will be as satisfactory as ^{75}Se - selenomethionine for pancreatic scanning.

Techniques of enhancing ^{75}Se - selenomethionine uptake by the pancreas are reviewed. An attempt to potentiate isotope uptake by the preparatory oral administration of purified soybean trypsin inhibitor in a further 30 patients was unsuccessful. The rationale of this approach is discussed.

It is concluded that ^{75}Se - selenomethionine pancreatic scanning is likely to become an important investigation in screening patients for the presence of pancreatic disease and in particular, carcinoma of the pancreas.

CONTENTS

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CHAPTER I

A REVIEW OF ATTEMPTS AT PANCREATIC VISUALISATION

The pancreas is one of the most inaccessible organs of the body and the diagnosis of the presence of pancreatic disease, particularly neoplasia and chronic pancreatitis, has remained a difficult and generally unrewarding challenge in clinical medicine. Its demonstration in everyday clinical practice depends mainly on the deplacements it produces of adjacent viscera such as the stomach, duedenum or kidney. A barium meal or pyelogram may provide indirect evidence of the presence of pancreatic disease.

Numerous attempts have been made to discover a simple technique of direct visualisation of the pancreas. In this chapter a review will be undertaken of the various attempts that have been made to opacify the pancreas.

Part 1. The Search for a "Pancreas Specific" Agent

a) Dyes

Following the observation of Crandall, Oldberg and Ivy (1929) that various dyes may concentrate in the pancreas, Ingraham and Visscher (1935) studied the excretion of industrial dyes from pancreatic fistulae in anaesthetised dogs. They grouped the dyes according to their electrochemical characteristics by determining the direction in which chromogen-bearing ions migrated in an electric field. This enabled them to discover that predominantly acid dyes, with the chromogen in the anion, appeared in the pancreatic juice. Wool blue G, fast fuchsin B, rhodamine B, acridine red, indigo carmine, eosin BS, basic fuchsin, flourescein and methyl red were excreted from the pancreatic duct in amounts varying from 0.5 to 5% of the blood concentration within a very short period. Acridine red and rhodamine B, though classified as basic dyes industrially, were found by the authors to be amphoteric in that they migrated partially to anode and partially to cathode.

In 1959 White and Magee attempted to exploit this information by opacifying the pancreas with the use of iodonated dyes. These authors found that acridine red appeared in pancreatic fistula catheters in dogs almost immediately after its intravenous injection. Simple iodination of acridine red markedly lessened its solubility but it still appeared promptly in the catheters. However, an area of opacity seen on x-ray was found to lie outside the pancreatic area when checked with metal markers. This led them to abandon their investigations with this substance. Similar results were obtained with a four-atom iodonated compound of acridine orange. The main problems to emerge were:-

i) the insolubility of the halogenated dyes made intravenous administration difficult if not impossible;

ii) the four-atom iodonated organic compounds particularly those of pyonin B were highly toxic to dogs;

iii) iodination of the molecule appeared to change its properties sufficiently to interfere with the ability of the pancreas to concentrate or excrete the dye.

In 1964, Desgrez, LeDoux-Lebard, Heitz, Atlan, Rosier, Behar and Aries reported the successful opacification of the pancreas by a tetra iodinated dye Erythrosine B. This compound is identical in structure to eosin differing only in that the bromine in eosin is substituted by iodine. It is soluble in both water and alcohol. These authors found they could obtain opacification of the pancreas of the cat without encountering severe side effects though a later study in dogs by Heitz, Premont, LeDoux-Lebard, Atlan, Behar, Leroy, Rosier, Frenoy, and Leger (1965) described the development of photosensitivities and urticaria following the intravenous injection of Erythrosine B. The physical characteristics and relatively low toxicity of this compound make it much more suitable than the iodinated dyes and metals previously studied for parenteral administration. However much more work will have to be done in order to confirm these studies and to define the precise value of the compound.

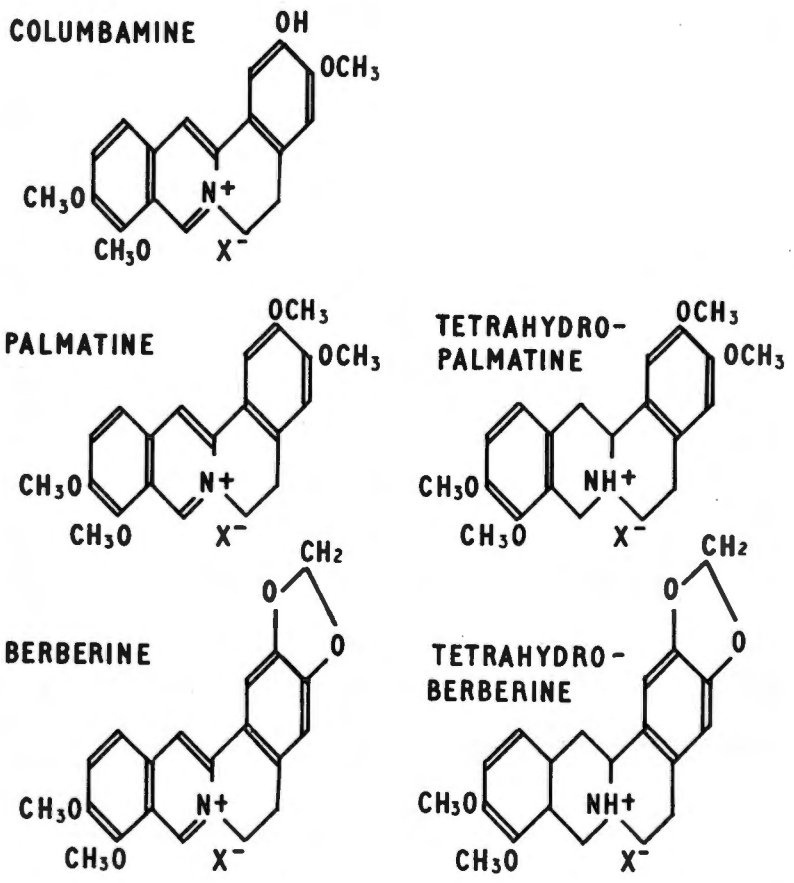

Fig.1.1: Berberine and related alkaloids prepared by Nardi and Seipel (1955) for pancreatic localisation. Page 7

b) Alkaloids

In 1955, Nardi and Seipal found that a subcutaneous injection of berberine, an alkaloid obtained by alcoholic extraction of Colombo root (Hydrastis) localized in the pancreas of rats and mice. The compound was detected in the pancreas 4 to 6 hours after administration by its characteristic bright yellow flourescence in ultra-violet light. No flourescence was noted in any other tissue. Twenty of the 22 berberine injected animals were found to have a high percentage of the injected dose (20 - 70%) in the panceas. They then went on to prepare some of the other related alkaloids (Fig. 1. 1.). Columbine, Palmatine and Berberine have a similar nuclear structure and differed only in their side chains. All yielded brilliant flourescence of the pancreas after parenteral injection. Tetrahydroberberine and tetrahydropalmatine have an identical nuclear structure differing from the parent compound only in the saturation of the second phenolic ring i.e. they are tetrahydro derivatives. The studies suggested that the nuclear structure of these compounds rather than their side chains was the important factor in pancreatic localization.

Iodination of the nuclear structure was attempted in 1960 by Blau and Bender who synthesized labelled berberine according to the scheme shown in Fig. 1. 2. Rats were sacrificed 30 minutes to 24 hours after subcutaneous or intravenous injection of the labelled berberine and the pancreas assayed. No more than 1% of the injected dose was located in the pancreas. Tissue extracts were examined spectrophotometrically and by flourescent microscopy. By the latter technique flourescence was apparent in frozen sections from liver, pancreas, kidney and spleen.

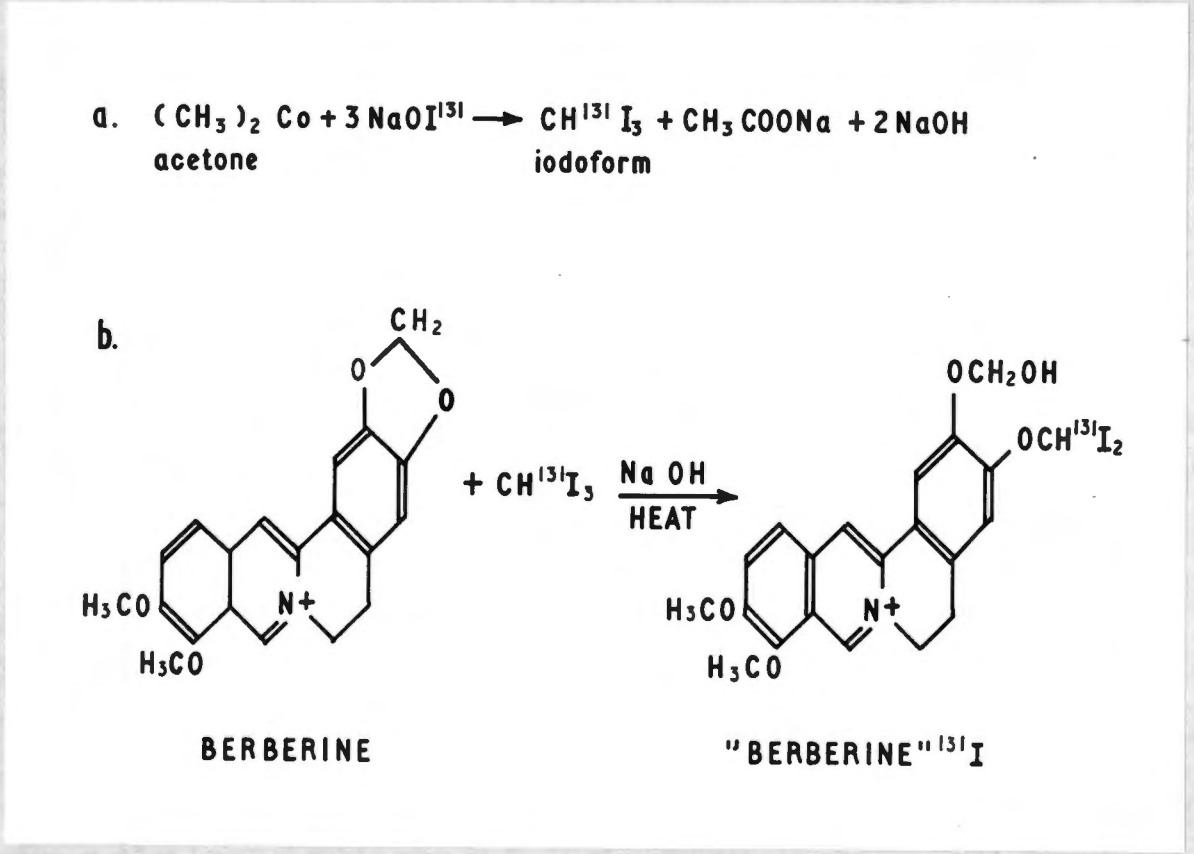

Fig.1.2: Scheme for the ^{131}iodination of berberine used by Blau and Bender (1960)

White and Magee (1959) in a limited study in two dogs failed to demonstrate berberine flourescence in the pancreas. Subsequently Rubaum and Shohl (1961) had no success with berberine in 6 dogs and could demonstrate only faint flourescence of the pancreas in rabbits. As a result of these studies the observations of Nardi and Seipal have fallen into disrepute. It is not clear why other workers have completely failed to repeaduce their apparently clear-cut results. It may be a question of species difference. Nardi and Seipal used mice whereas other workers have used rats, dogs and rabbits. In addition the process of iodination may change the physical properties of the compound sufficiently to alter its biological behaviour.

c) Antibiotics and Chemotherapeutic Agents.

Howard, Pulaski and Fusillo (1952) studied the pancreatic secretion of antibiotics and sulphadiazine in man and reported that sulphadiazine appeared promptly in the pancreatic juice. Initially the concentration in the juice was approximately equal to that in the serum. Sodium penicillin also appeared in therapeutic concentrations but streptomycin, aureomycin, terramycin, chloramphenicol and polymyxin were excreted poorly. This observation has been confirmed by Johnson and Peskin (1965) with an iodinated preparation of sulphadiazine but no further information is given by these authors besides the statement of this fact.

As part of a larger study on the pancreatic localisation of various radioactive heavy - metal compounds Meschan, Quinn, Witcofski and Hosick (1959) reported that zinc sulphadiazine (^{65}Zn) localized poorly in the pancreas.

d) Heavy Metals

Zinc

In 1927 Drinker, Thompson and Marsh reported the accumulation of zinc in the pancreas, liver, gall-bladder and kidney of cats fed dietary supplements of zinc oxide. The pancreatic content was particularly impressive being 10 to 20 times that found in control animals. In 3 of 10 cats, there was an associated heavy fibrous change in the acinar tissue of the pancreas. These observations were substantiated by Scott and Fisher in 1938 who fed cats a zinc supplemented diet for 3 to 4 months and noted that the pancreas became hard, gritty and fibrotic. The islets appeared to be unaffected.

In more detailed distribution studies of the metabolism of zinc utilising the radioactive isotope ^{65}Zn, Sheline, Chaikoff, Jones and Montgomery (1943) showed the percentage concentration to be highest in the pancreas, followed by the liver and kidney. The distribution pattern was similar in mouse and dog. After a single injection about 11% of the zinc was eliminated by the external secretion of the pancreas over a period of fourteen days. This observation suggested that zinc probably accumulated in the acinar cells and was excreted gradually in the pancreatic juice.

In an attempt to exploit the tendency of zinc to accumulate in the pancreas Shapiro (1957) prepared a number of halogenated zinc compounds which he tested in rabbits. Although he achieved a limited success in producing opacification of the pancreas he was discouraged from further study for a number of reasons: -

i) All the tetra-iodinated organic compounds studied showed pronounced toxicity;

ii) Most of the organic halogenated zinc derivatives studied were unstable, tending to precipitate out;

iii) All heavy metals, including zinc were toxic in ionic form in the concentrations necessary to produce satisfactory radio-opacification. Unfortunately the author gave no chemical details of the halogenated zinc derivatives which he administered. It is of interest that the problems of toxicity and insolubility are very similar to those encountered when attempting to halogenate dyes.

Manganese

Sheppard, Wells, Hahn and Goodell (1947) showed that after a single injection of ^{54}Mn - manganous chloride in the dog, moderate concentrations were located in the pancreas. This observation was confirmed by Burnett, Bigelow, Kimball and Sheppard (1952) in the mouse and dog, though in rats the concentration in the pancreas was found to bexceed that of the liver by at least three fold, the peak height in both being equivalent to about 6% of the injected dose.

In an attempt to visualize the pancreas Meschan, Quinn, Witcofski and Hosick (1959) used manganese chloride (both ^{54}Mn and ^{52}Mn); zinc chloride (^{65}Zn); zinc sulphadiazine (^{65}Zn) and a zinc complex of 3' and 6' aminoflourescein. After a single intravenous injection of about 100μCi of the compound, external counts were taken over the pancreas at 8 to 24 hours. The results with ^{65}Zn sulphadiazine and ^{65}Zn 3" or 6' aminoflourescein closely resembled those of inorganic Zn. The curve for zinc resembled the manganese

curve but the former showed a greater pancreatic activity. However the authors concluded that scintiscan studies were not of sufficient detail to be applicable either clinically or experimentally.

Part 2. Islet - Cell Opacification

In their review on pancreatic visualisation Peskin and Johnson (1965) stated that unsuccessful attempts had been made to opacify the islets of Langerhans through halogenation of alloxan. Apart from the practical difficulties associated with the use of alloxan, Shapiro (1957) stressed that it was unsound theoretically; the islet cell mass comprises only 2 - 3% of the total pancreatic mass and is not uniform in distribution throughout the pancreatic parenchyma.

Part 3. Radiological Procedures

a) Direct Techniques

i) Intraductal Contrast Medium

Direct intraductal injection of contrast media was first performed by Doubilet and Mulholland in 1947 but only reported in 1955. These authors obtained opacification of the pancreas by injecting 70% Diodrast (Diodine) through polyvinyl tubing placed in the main pancreatic duct at operation. They noted that opacification of the pancreas tissue occurred only in the presence of acute inflammation and that in its absence the ducts alone were visualised. This technique provided a means of assessing more precisely the state of the pancreas at operation but it carried the definite risk of inducing an attack of acute pancreatitis. A variation introduced by Hayes (1960) involved the injection of contrast medium through a polythene catheter placed in the cystic duct at the time of cholecystectomy. To obtain a pancreatogram, 10 15 mgs. of morphine was injected intravenously 10 seconds before the introduction of 10 ml. of radio - opaque medium. This resulted in reflux of the medium into the pancreatic duct due to spasm of the Sphincter of Oddi. The author claimed to have obtained 14 good quality pancreatograms in 18 patients of which 3 had demonstrable disease. Utilising the same principle, Silverman and Hill (1963) injected cholografin (Iodipamide methylglucamine) intravenously and 2½ hours later 15 - 20 mgs. of morphine. Twenty minutes after the morphine 75 u of cholecystokinin was injected intravenously and serial plain films and tomograms were taken after 45 minutes. Visualisation of the pancreatic duct was not accomplished in any subject. Extrusion of the dye through the sphincter was the rule.

In 1965, Rabinov and Simon accomplished the remarkable feat of peroral cannulation of the Ampulla of Vater, achieved with a specially designed duodenal tube. In the patient described they achieved satisfactory opacification of the common bile duct and the main pancreatic duct. It is undoubtedly significant that their technique failed in seven other patients suffering from a variety of pancreatico - biliary diseases. These authors have demonstrated that it is possible to cannulate the Ampulla of Vater perorally but with available techniques the almost certain prospect of failure is sufficient to discourage most radiologists from even trying.

In 1967 Waldron, Bragg, Daly and Seamon working on dogs, placed intraluminal balloons in the duodenum to isolate the segment containing the opening of the biliary and pancreatic ducts. Reflux of contrast medium was effected from the duodenum into the biliary and pancreatic duct systems using aminophylline intravenously and Xylocaine (Lidocaine hydrochloride) locally in the isolated portion of the duodenum. They had greater success in filling the biliary system (5 out of 7 times) than they did the pancreatic duct (2 out of 7 times). However it has yet to be demonstrated that a similar technique may be successfully applied to humans.

ii) Angiography

Per Ödman's (1958) study of selective angiography of the coeliac artery is probably the finest study to date on visceral angiography including the pancreas. It is apparent from his work that meaningful results require considerable skill and experience as well as specialised equipment.

In 1959 McCune and Stanbro attempted to improve the arteriographic

demonstration of the pancreas by increasing the permeability of the pancreatic vasculature. They based their experiments on the earlier work of Stein, Powers and Browne (1956) who demonstrated Indian ink staining of the interlobular stroma of the pancreas following intravenous injection of Trypsin. Indian ink alone had no effect. McCune and Stanbro injected 1 to 10 mg. of crystalline trypsin and Indian ink into the pancreatico - duodenal artery of anaesthetised mongrel dogs. Within 5 to 20 seconds there was visible darkening of the pancreas. Provided the dose of Trypsin injected was kept below 5 mgs., pancreatitis and vascular thrombosis was avoided. The experiments were then repeated with 90% hypaque (Diatrizoate sodium). Diffuse opacification of the pancreas was obtained and the degree of visualisation increased for up to 30 minutes after injection. Injection of contrast medium alone produced a simple arteriogram of the pancreatic vessels. Intra - aortic injection of trypsin and contrast medium with the catheter tip placed 3 centimetres above the site of origin of the hepatic artery resulted in some opacification of the pancreas in 70% of 16 dogs. The potentially dangerous side effects of intra-arterial injection of trypsin has deterred the use of this technique in humans.

Boijsen (1968) studied the effects of adrenaline and bradykinin injection on the pancreatic vasculature. Selective coeliac and superior mesenteric angiograms were performed before and after infusion of adrenalin and bradyknin into these vessels. Bradykinin caused a marked increase of flow through all vasculature beds within the coeliac and superior mesenteric territories and thus also through the pancreatic arteries. The angiographic detail was poor after bradykinin as a consequence of the increased flow. Adrenalin, on the other hand, caused a marked constriction of gastric, splenic and hepatic arteries while the pancreatic vessels dilated. Although the flow of contrast medium through the pancreas appeared more rapid, the angiographic detail was definitely enhanced.

iii) Transverse Axial Stratigraphy

Giraud, Bret and Gostaz (1954) employed the technique of transverse axial stratigraphy in the examination of the pancreas. Retro-peritoneal and gastric insufflation provided the contrast, the pancreatic image being visible on sagital exposure as an oval, triagular or pyriform density. Optimum clarity was usually obtained by vertical tomography, taking "cuts" at different levels. The authors stressed that the technique had special value in lesions of the body and tail of the pancreas. However, like angiography it would require considerable experience for accurate interpretation of the picture obtained.

b) Indirect Techniques

i) Barium Meal

Barium meal examination of the upper gastro - intestinal tract has remained the mainstay of radiological examination of the pancreas in general clinical practice from the earliest reports in the second decade of this century (Dorner 1915; Case 1916) up to the present time (Salik 1961; Poppel 1954). This approach is unfortunately an indirect one and will only reveal grosser forms of pancreatic pathology. In addition, the signs of underlying pancreatic disease demonstrated by barium meal tend to be non-specific, a fact emphasised by Frostberg in 1938 in his classical description of the inverted "3" sign, occurring in cases of Vaterian and pancreatic carcinoma. However with attention to more subtle detail Salik was able to claim a diagnostic accuracy of 77% out of a series of 64 patients with pancreatic carcinoma. This must represent one of the more successful diagnostic series as Berk and Haubrich (1965) in a review of 9 published reports on barium study in carcinoma of the pancreas found a 43.8% mean success rate out of a total of 810 cases. This latter figure is probably more representative of the diagnostic accuracy of barium meal in carcinoma of the pancreas in the less specialised institutions.

The value of barium studies in pancreatitis is much more difficult to determine accurately. However attention to more subtle radiological changes emphasised in recent years by Poppel (1954) will increase the diagnostic value of this procedure. With considerable experience in the radiology of pancreatitis Poppel has emphasised the value of duodenal mucosal oedema (including the "papillary sign" due to oedema of the papilla at the Ampulla of Vater), doudenal irritability, widening of the

duodenal loop and pressure on the inner concave border of the duodenum.

ii) Percutaneous Splenoportography

In 1955 Figley, Fry, Orebaugh and Pollard observed that percutaneous splenoportography was of value in assessing disease of the pancreas. Thrombosis or distortions of the splenic vein could occur in pancreatitis, carcinoma or with pseudocysts of the pancreas.

iii) Pyelography

Various case reports have appeared from time to time describing pyelographic changes due to primary pancreatic disease (Ormond, Wadsworth and Morley, 1942; Chamberlain and Imber, 1954).

Part 4. Conclusions

The acknowledged poor prognosis following the diagnosis of pancreatic carcinoma, excluding ampullary carcinoma (Avery Jones and Gummer, 1960) must reflect in part at least the inadequacy of the available diagnostic techniques. For example, of 100 patients with pancreatic carcinoma followed by Burk and Haubrich (1965) only 5 patients survived 18 months from the time of diagnosis.

In the last resort the clinician has still to depend in most cases on barium meal changes for visible evidence of pancreatic disease. If the clinical suspicion of pancreatic disease is sufficiently strong and particularly if carcinoma is suspected, arteriography may be attempted. However a laparotomy is often the next diagnostic step as even angiography may be uninformative.

The use of pancreatic function tests and cytology may be of value in experienced hands but these too may be misleading.

The advent of a method for pancreatic scanning (Blau, Manske and Bender, 1962) offered the hope of a simple procedure, causing very little discomfort to the patient, which could demonstrate the whole pancreas in situ.

CHAPTER 2

PHANTOM PANCREATIC STUDIES

Phantom studies were undertaken under simulated conditions in order to calculate the effects of a number of variables upon the pancreatic scan. The information derived from these studies would assist both in helping to determine the optimum machine settings for the scanning of ^{75}Selenium (^{75}Se) and in interpretation of the pancreatic scan.

As a retroperitoneal organ the pancreas is generally thought to be immobile. On theoretical grounds at least, this immobility of the pancreas on the posterior abdominal wall plus the fact that it is a thin organ should enhance the diagnostic value of a scan provided the isotope uptake by normal pancreatic tissue is sufficient to be detected from the body surface. A thin organ in one plane, situated at the optimum focal distance to the scanning head should permit optimum assessment of the state of that organ. With displacements of any part of the pancreas cephilad or candad the organ would still retain the same plane (with the patient supine) and therefore remain in focus of the scanning collimator. However there are situations in which the optimal distance between the collimator and the pancreas is likely to be disturbed. Even with a focussing collimator the count rate from a radioactive source in the body falls off sharply as the depth of the source is increased. Thus if part of the pancreas (for example, head or tail) is situated at a greater depth in the body than the rest of the organ through displacement the impression might falsely arise of poor uptake in that part even if the activity were uniformly distributed throughout the pancreas. Also, in an obese patient the pancreas - collimator distance may perforce be greater than the desired optimum. The whole pancreas would therefore be out of focus.

Part 1. Aims of Study

The principal aims of this study were:-

i) To determine the optimum machine settings on the scanner (to be used for the clinical studies to be reported) for scanning of the isotope ^{75}Selenium (^{75}Se); and

ii) To study the effects of variation of the position of part or the whole of the pancreas on the pancreatic scan.

Part 2. Material

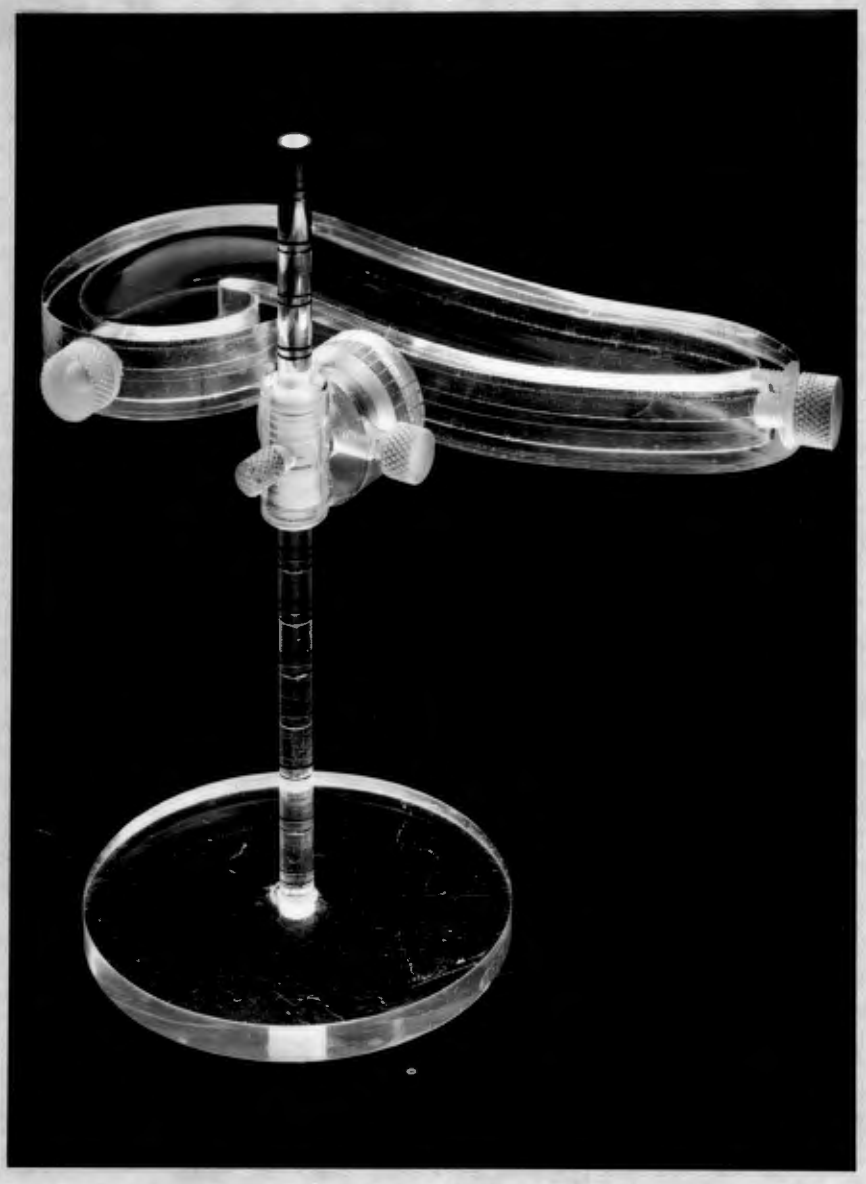

Fig.2.1: Perspex phantom pancreas and stand. The black horizontal stand markings are spaced at 1 centimetre distance. Page. 31 .

i. Scanning Machine

The scans were performed with the Picker Magna Scanner V (Picker X-Ray Corporation, New York) (Fig.3. 2) which has a 12.5 cm. diameter thalium activated Sodium Iodide crystal and prints out the scan record both as an eight - colour dot scan and as a "photoscan" recorded on standard 36 x 43 cm. x-ray film. An 85 hole collimator of nominal focal length 12 cm. and a scanning speed of 24 cm./minute were used for the phantom studies.

ii) Phantom Pancreas

A phantom pancreas and stand (Fig.2.1) were constructed out of perspex.

The phantom (Fig.2.1) measured 13½ cm. along its long axis and 5½ cm. across the widest part of the head at right angles to the long axis (cavity measurements). The lumen was 1 cm. thick. Two perspex screws, at the tip of the tail and on the inferior margin of the head, permitted easy filling of the phantom with solution. The capacity when full being 50 ml. of water. It was attached to the vertical stand by a perspex connection which permits rotation of the body of the phantom around an axis running in the line of the connecting piece (Fig.2.2). Thus while maintaining the same level the head of the pancreas may be raised while the tail is lowered and vice versa. In addition the level of the phantom may be adjusted on the vertical stand which is marked at centimeter intervals (Fig.2.1).

iii) ^{75}Se - Selenomethionine

The selenoamino acid, ^{75}Se - selenomethionine was used. This was obtained from "The Radiochemical Centre", Amersham. The radioisotopic purity was confirmed by the manufacturers who stated that no other gamma-

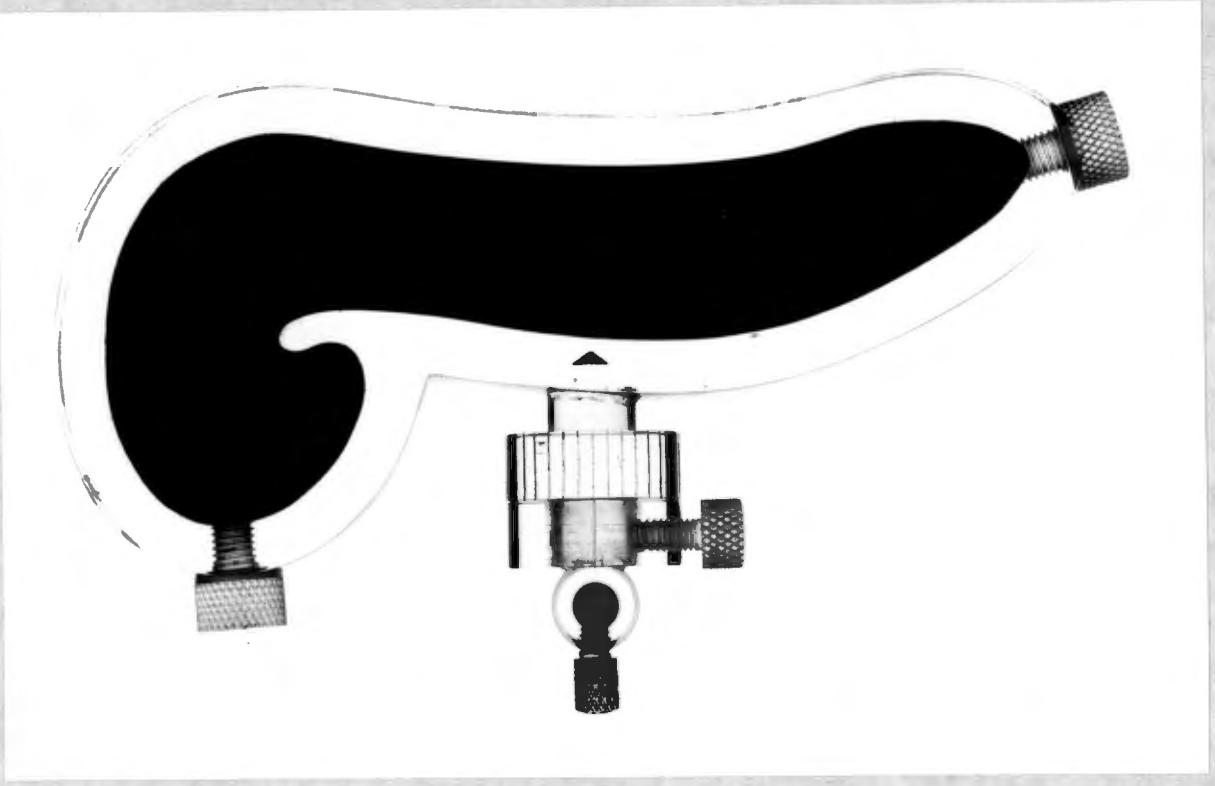

Fig.2.2: Indian-ink filled phantom viewed from above. The graduated stand connecting-piece permits rotation of the phantom through 360°.
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emitting isotopes had been detected in the freshly prepared material, or in old stocks which had decayed for more than 2 half- lives.

Part 3. Methods

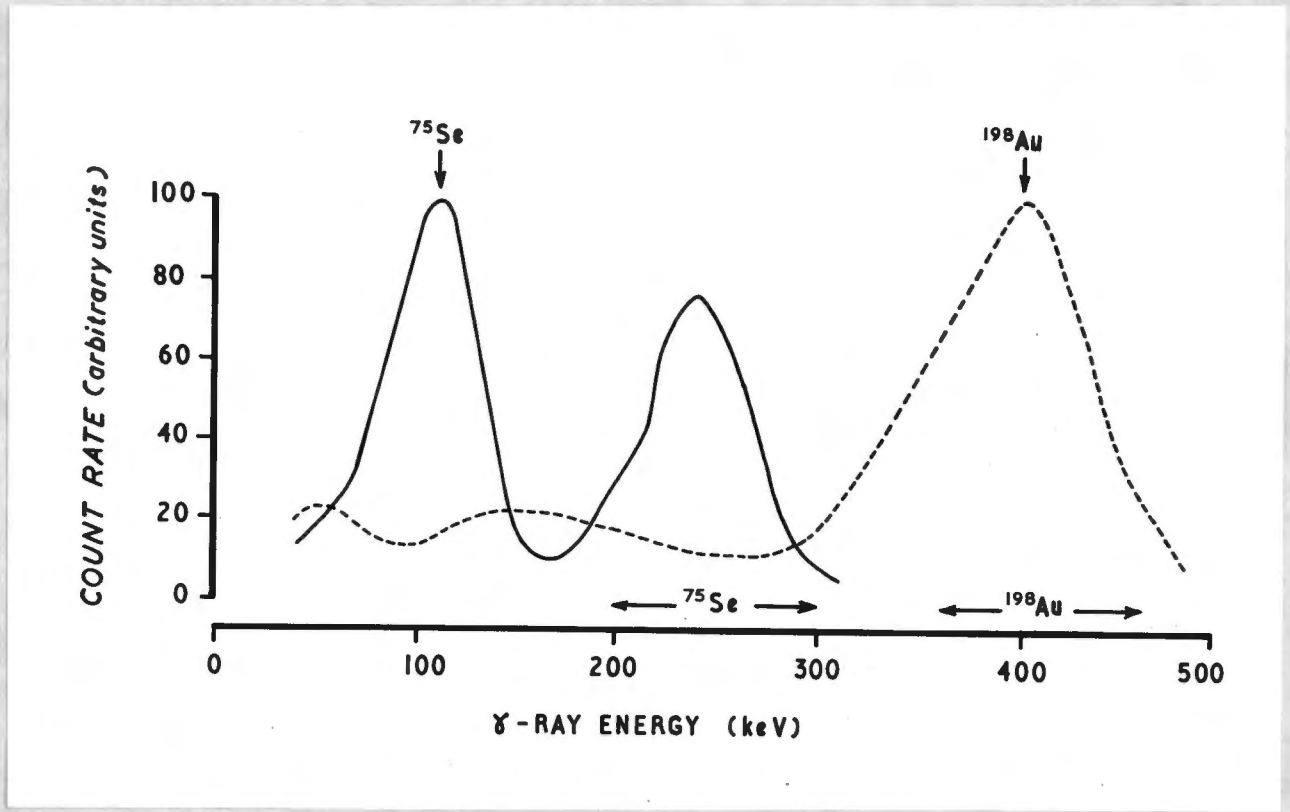

Fig.2.3: The gamma-ray energy spectrum of ^{75}Se and ^{198}Au as determined on the Picker Magna Scanner V. Page. 36 .

i) To Determine the Gamma - Energy Spectrum of ^{75}Se on the Picker Magna Scanner V

A sealed bottle containing 10μCi of ^{75}Se - selenomethionine was placed at 12.5 cm. from the collimator in its long axis. The high voltage applied to the photomultiplier of the scanner had previously been adjusted so that the threshold and channel width scales of the pulse height analyser section of the machine could be read directly in keV. The channel width was set at 20 keV and readings were taken of the count rate (in counts per minute read from the ratemeter display) at threshold values from 40 to 320 keV. Taking the highest single reading as 100% a graph was plotted of the variation of count rate with threshold setting or, in effect, the gamma - ray energy spectrum ^{75}Se (Fig.2.3).

A similar spectrum was determined for ^{198}Au. The significance of this is explained in Chapter 3 under "^{198}Au - colloid gold liver scans".

ii) To Determine, a) The Optimum Gamma - Energy Spectrum for Pancreatic Scanning, and b) The Effect of Increased Collimator - Pancreas Distance on the Appearance of the Scan.

The phantom pancreas was filled with a solution containing approximately 20μCi of ^{75}Se - selenomethionine. This would correspond to 8% of an average adult dose of 250μCi and probably represents the portion taken up by the human pancreas under optimum conditions (Chapter 3). The phantom was placed in a water - bath as illustrated diagrammatically in Fig.2.4 . The water would absorb some of the radiation emitted by the isotope, thus simulating absorption in the body.

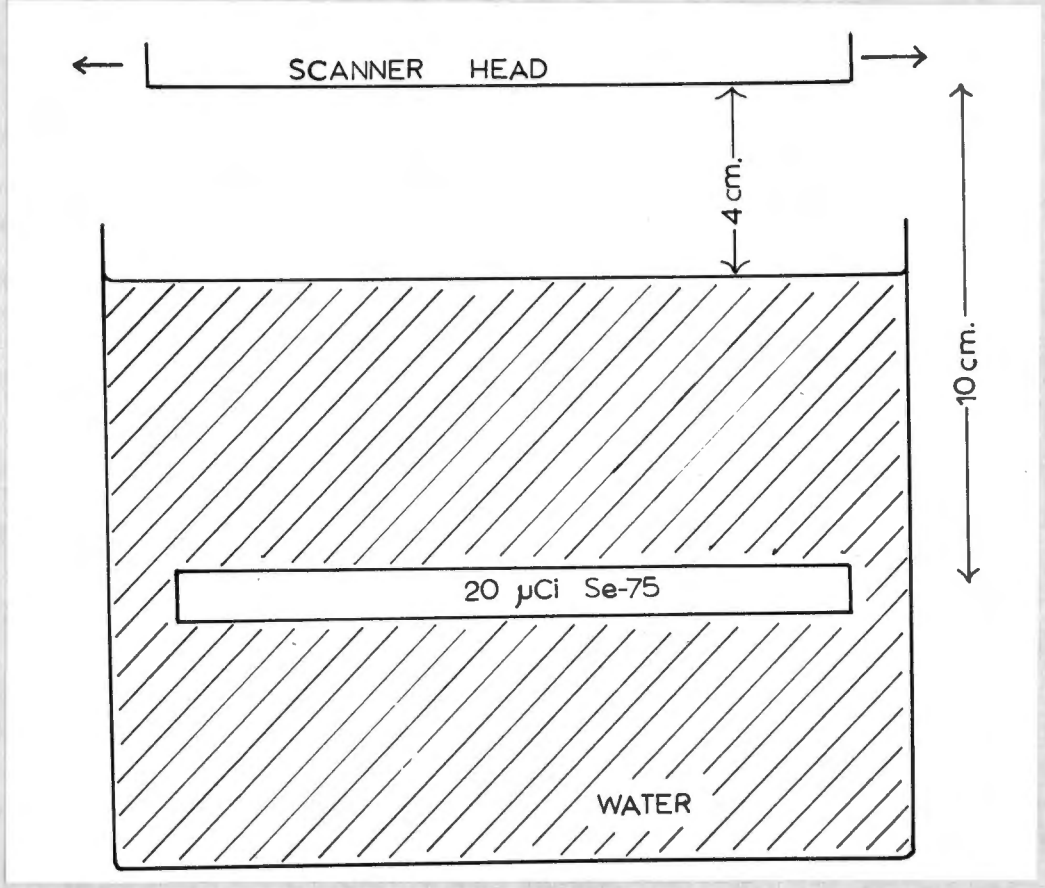

Fig.2.4: Diagrammatic representation of the phantom pancreas in the water-bath. The figures given relate to experiment b)ii. Page 38 .

a) For the first part of the experiment the pancreas was placed at an optimal distance of $12\frac{1}{2}$ cm. from the collimator. The distance from the immersed phantom to the water surface was $8\frac{1}{2}$ cm. and from the water surface to the scanner head, 4 cm.. The scanner was run at 24 cm./minute. Two scans were performed. In the first the machine was set to detect only radiation of energies between 220 to 320 keV. The second scan was repeated under identical conditions but the settings were changed to 100 - 320 keV. On the first scan the higher energy peak alone was detected. On the second, both energy peaks were utilised.

b) (i) To determine the effect of increased distance between the pancreas and the scanner head the phantom was lowered 6 cm. in the water bath. This increased the collimator - pancreas distance to 18 cm. and the pancreas to water - surface distance to 14 cm.. Two scans were performed at the same two machine energy settings described above.

b) (ii) To assess the influence of displacement of the pancreas on the scan the phantom was placed in the water - bath at a distance of 10 cm. from the collimator and 6 cm. from the water surface (Fig.2.4). The scanner was set to detect radiation of energies between 220 keV and 320 keV. The pancreas was scanned at 24 cm./minute in the horizontal position (Fig.2.7), with the head of the pancreas tilted up by 45° (Fig.2.8) and with the tail of the pancreas tilted up by 45° (Fig.2.9).

Part 4. Results

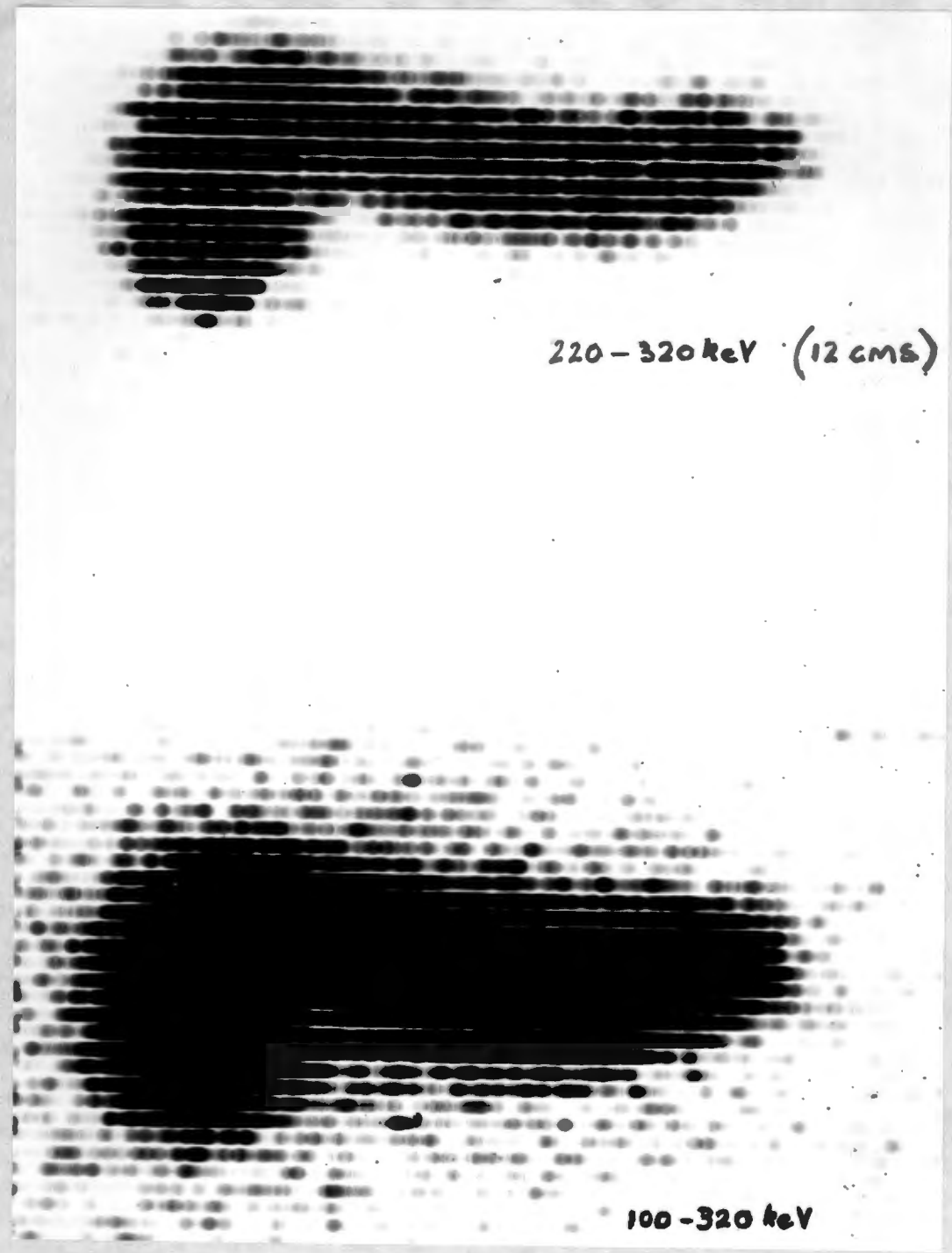

Fig.2.5: Page.38

1. The gamma - energy spectrum of ^{75}Se recorded on the Picker Magna Scanner V.

The graph depicting the energy level on different machine settings is shown in Fig.2.3 . The results for ^{198}Au are shown on the same graph. It can be seen that the two maximum peaks for ^{75}Se coincide with the 110 and 240 keV energy levels.

The maximum ^{198}Au energy peak occurs at 400 keV.

2. The results of the pancreatic scan at different energy levels and the effects of varying the pancreatic - collimator distances will be presented together.

In Fig.2.5 with the pancreas at an optimal distance of 12 cm. from the collimator, the scan is well shown with both sets of energy settings. However, the pancreatic image on the 100 - 320 keV machine settings is considerably enhanced (Fig.2.5 lower) when compared to the image on the 220 - 320 keV settings (Fig.2.5 upper).

With the phantom at 18 cm. from the collimator the pancreatic image is much better recorded on the 100 - 320 keV settings (Fig.2.6 lower) than it is with the 220 - 320 keV settings (Fig.2.6 upper).

In tilting the phantom the altered pancreatic image recorded is clearly depicted in the colour scans shown in Fig.2.8 and Fig.2.9 .

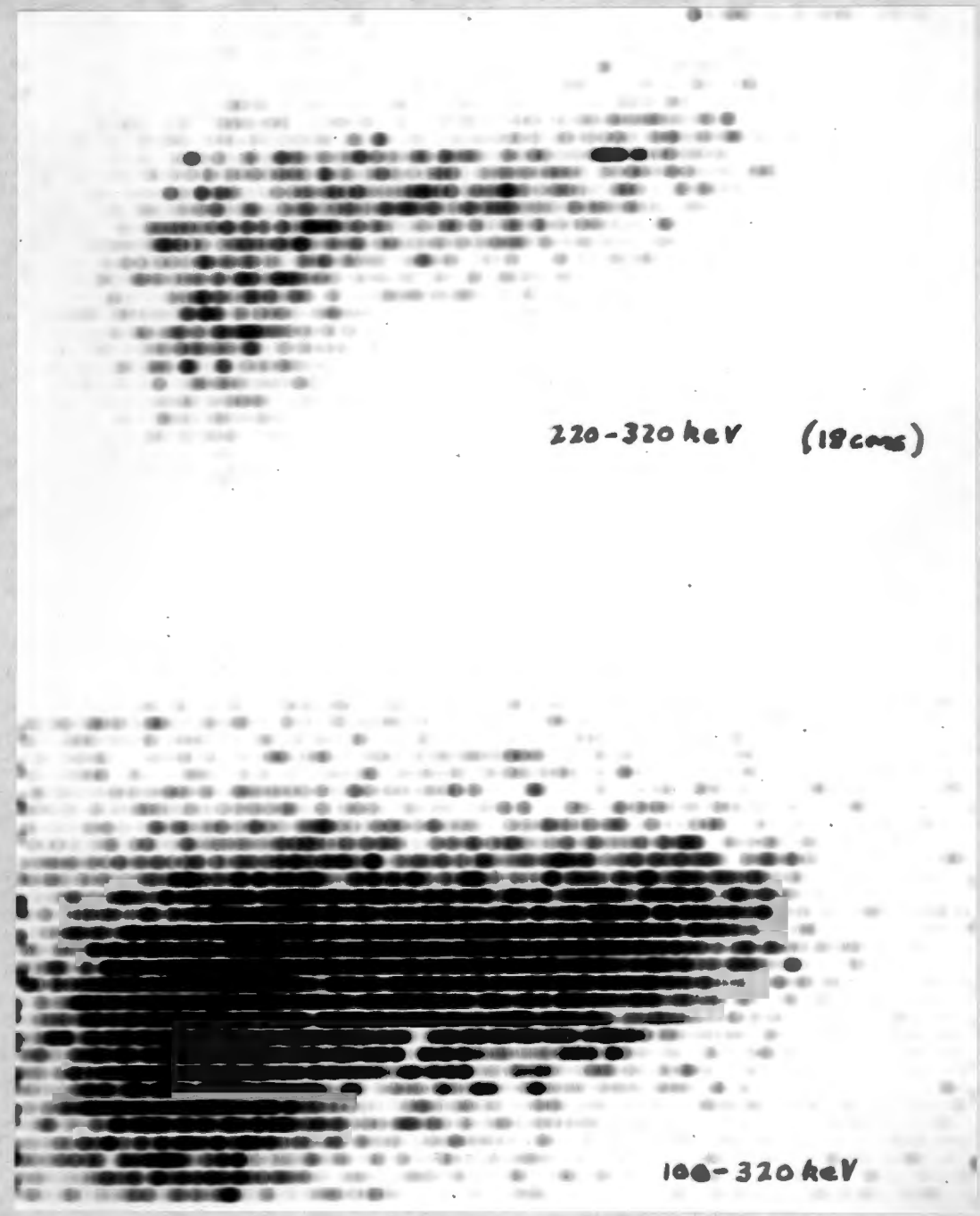

Fig.2.6: Page 38 .

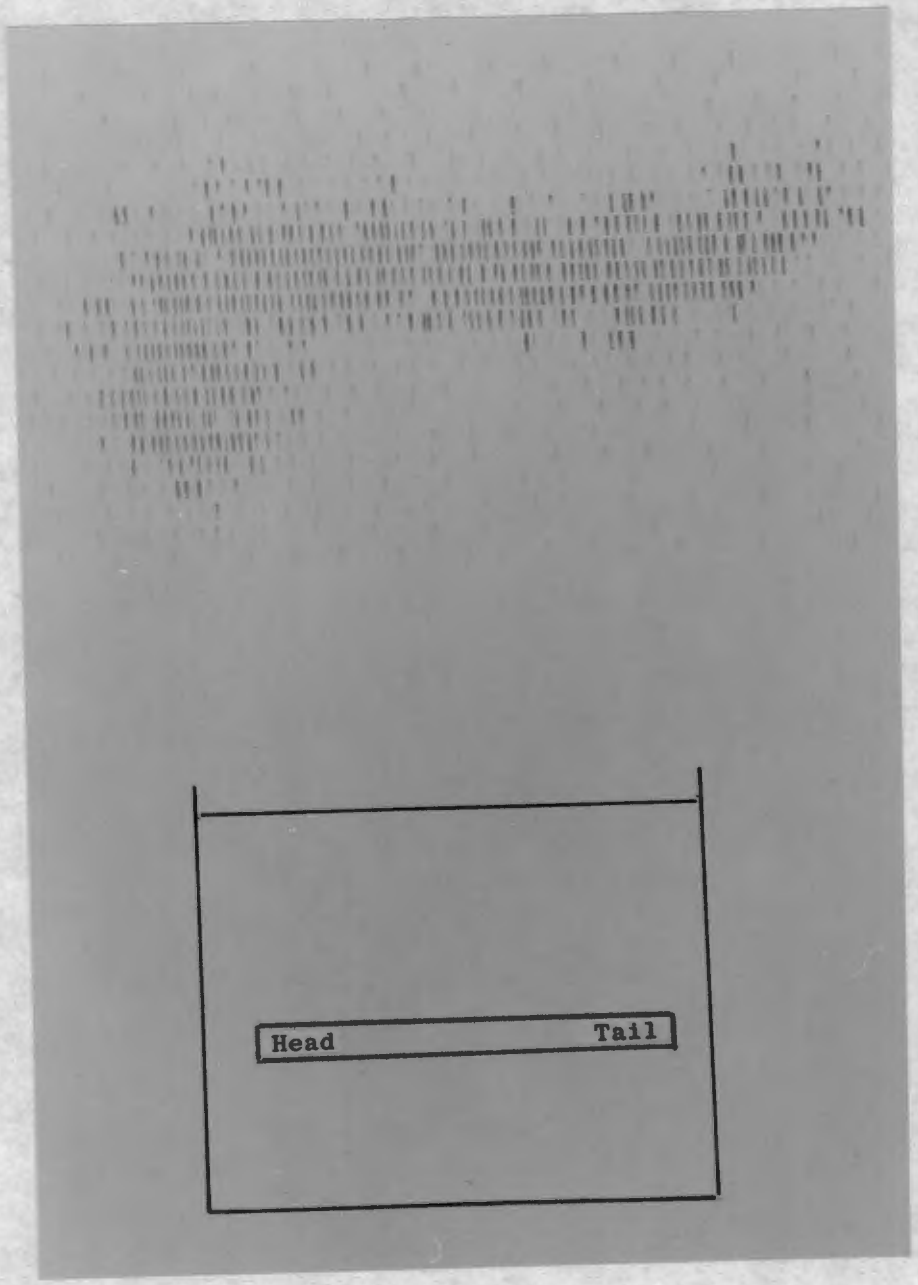

Fig.2.7: Colour-scan of phantom in the horizontal position. Machine settings 220 to 320 keV. Page 38 b)ii.

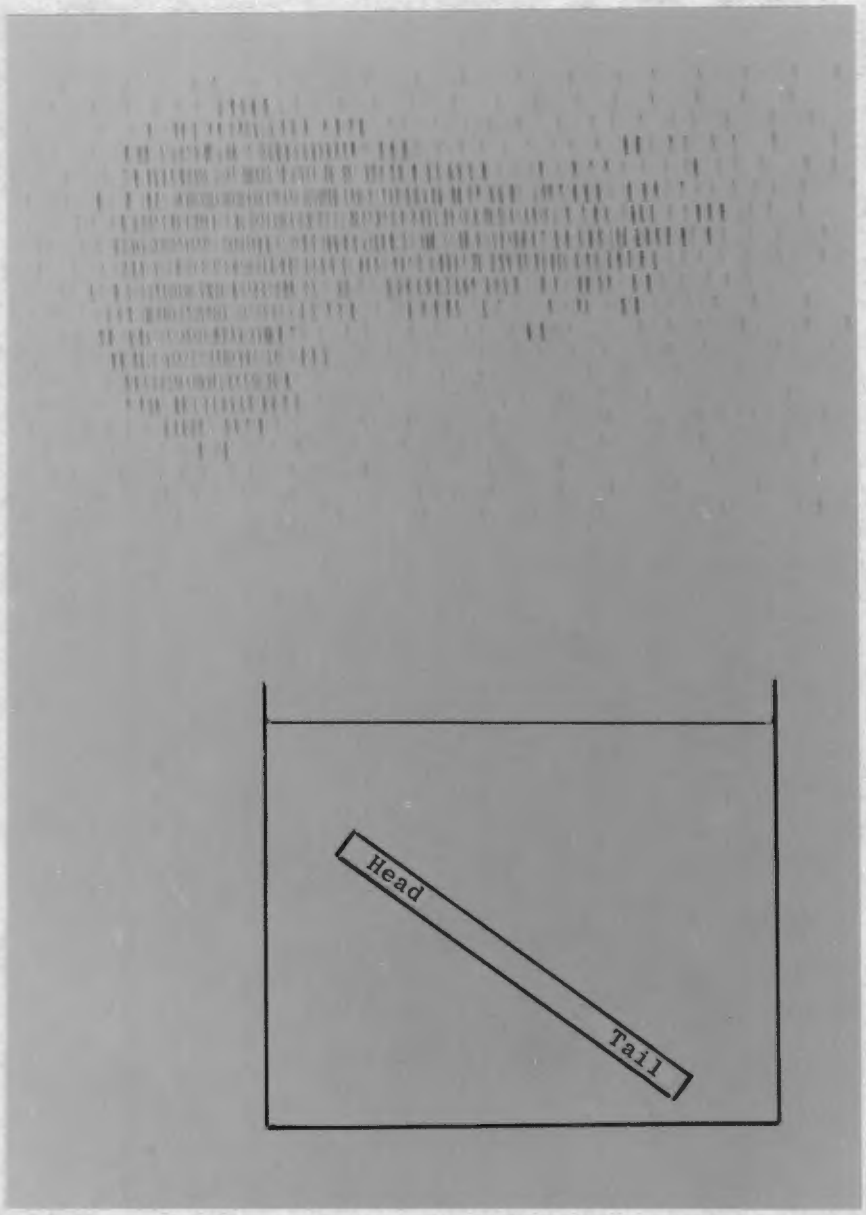

Fig.2.8: Colour scan of phantom with head tilted up 45°.
(Machine settings same as Fig.2.7.)
Page 38 b)ii.

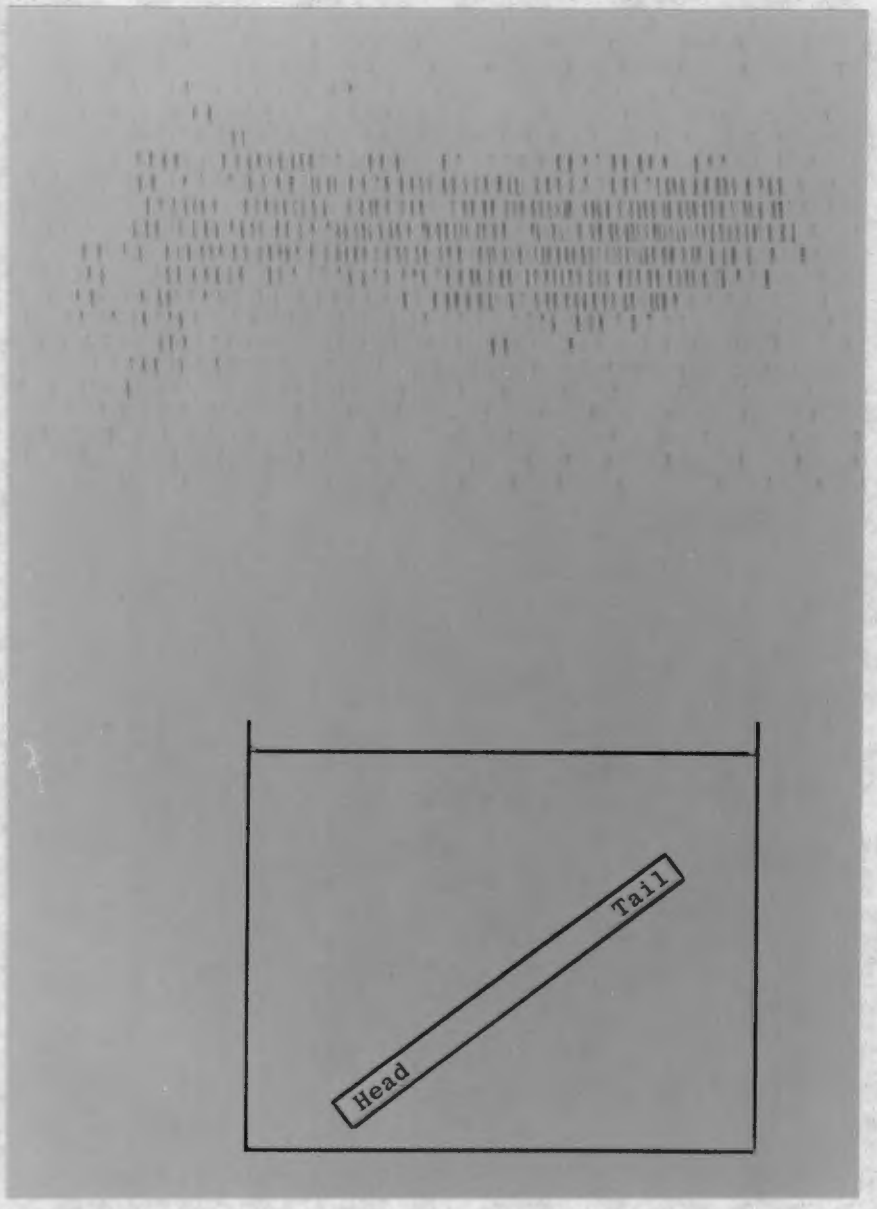

Fig.2.9: Colour scan of phantom with the tail of the pancreas tilted upwards by 45° (machine settings same as Fig.2.7.).
Page 38.

Part 5. Discussion

On the basis of these results it was decided that all patients (unless very obese) would be scanned with the machine settings of 220 to 320 keV. This decision was based on the following reasoning. Firstly, with the pancreas being a fairly deep seated organ the higher energy peak (Fig.2.3) was likely to give a better scan impression than would the lower peak. Under optimum conditions, the inevitable uptake of ^{75}Se - selenomethionine by the adjacent liver would, on the broad 100 to 320 keV machine settings, be associated with much greater scatter. This it was felt would tend to reduce the clarity of the pancreatic image. In addition the inevitably higher count rate from the 100 to 320 keV settings could obscure a small lesion in the pancreatic parenchyma. The difference in image density at the different energy setting is strikingly apparent in Fig.2.5 . The narrow 220 to 320 keV settings gave a less intense but quite clear impression under optimum conditions (Fig.2.5).

With an increased distance between pancreas and collimator on the 220 - 320 keV settings there was a striking reduction in the intensity of the image (Fig.2.6). Under these conditions (for example, with a very obese patient) the pancreas may have to be scanned on the broader spectrum machine settings before a diagnosis of "reduced uptake" is made.

The scan effects produced by tilting the phantom are of interest. A more accurate representation of events would be shown if it were possible to "displace" the head of the phantom towards the collimator without simultaneously displacing the tail away (or vice versa) as the pancreas is not a rigid organ. In any case movement in a posterior direction would be limited by the posterior abdominal wall. However the similarity in appearance between the phantom scan (Fig.2.8)and the patient scan 6 hours after the isotope injection, discussed in Chapter 3 (Fig.3.3b), is striking.

Part 6. Conclusions

A number of simple phantom studies have assisted in determining the effects of variation in the ^{75}Se gamma energy spectrum selected for scanning purposes.

The effects of the variations in the distance between part or the whole of the phantom pancreas and the collimator are recorded. Although the higher energy peak of ^{75}Se was selected for the human pancreatic scan, it was apparent that with a large pancreatic - collimator distance, a broader setting which incorporates both energy peaks would be necessary.

CHAPTER 3

AN ASSESSMENT OF THE ^{75}Se - SELENOMETHIONINE PANCREATIC SCAN

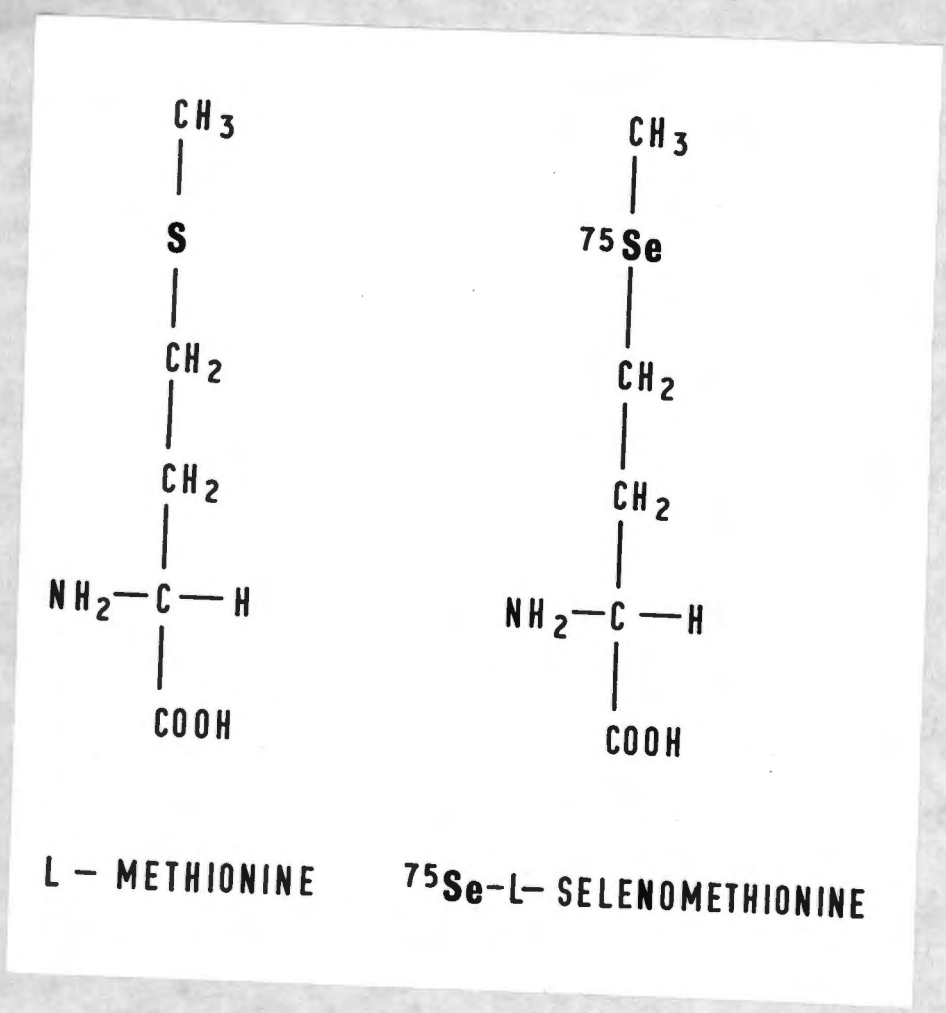

Fig.3.1: Page 51 .

i) Rationale of Pancreatic Scanning

Radioisotope scanning of the pancreas provides a method of visualizing the pancreas in situ by surface scanning of the abdomen after the administration of a radioactive labelled amino-acid which is incorporated into the proteins synthesized by the pancreas (Hansson and Blau, 1963). The amino-acid used in this study is ^{75}Se - L - selenomethienine, an analogue of methionine in which the normally occurring sulphur atom is replaced by ^{75}Selenium (^{75}Se) (Fig.3.1). The physiology of selenomethionine incorporation by the pancreas reflects the normal capacity of the exocrine pancreas for a high specific uptake of circulating amino-acids utilised in the synthesis of digestive enzymes.

There have been a number of reports of high amino-acid uptake by the pancreas shortly after the administration of labelled amino-acids. (Friedberg, Tarver and Greenberg, 1948; Maass, Larson and Gordon, 1949; Busch and Greene, 1955; Kukral, Adams and Preston, 1965; Sternberg and Imbach, 1967). All amino-acids tested show a high localisation in the pancreas 1 to 3 hours after administration (Table 3.1).

Table 3.1

Pancreas Localisation of Amino - Acids One Hour After Intravenous Administration (Blau, 1964)

Amino Acid	Proportion of Dose in Pancreas (%)	Pancreas (Per Gm.) / Liver
^{14}C - L - methionine	6.0	8.8
^{35}S - L - cystine	5.1	7.2
^{14}C - DL - tryptophan	12.5	11.2

Wheeler, Lukens and Gyorgy (1949) have demonstrated that this high rate of amino-acid incorporation is principally a reflection of functioning acinar tissue. These authors found that in the duct-ligated cat pancreas where the acinar tissue is atrophic but in which the islet cells are physiologically intact, incorporation of ^{35}S - methionine was considerably lower than in the normal pancreas. The pancreatic activity due to ^{35}S - methionine uptake was related to the degree of tissue atrophy and where atrophy was incomplete, the activity found was intermediate between that of normal and atrophic tissue.

The principal function of the pancreatic acinar cell is the synthesis and secretion of digestive enzymes. Siekevitz and Palade (1960) have calculated that the rate of turnover of the zymogen protein is 10 to 20 times as great as that of the non-exportable acinar cell protein. That the zymogen protein represents the digestive enzymes is now well established. Keller and Cohen (1961) for example, demonstrated that the chromatographic elution profile of the proteins of bovine zymogen granules is almost identical to that obtained with the proteins of pancreatic juice. In addition, the relative proportions of the protein components of the zymogen granules were strikingly similar to those of the pancreatic juice.

The rapid utilization and destruction of the pancreatic digestive enzymes requires a rapid rate of synthesis by the pancreas and accounts for the high amino acid uptake. Kukral, Adams and Preston (1965) point out that the pancreas, with about 2.5% of the weight, manufactures approximately the same amount of protein each day as do both the liver and reticulo-endothelial system in maintaining the blood protein levels. They calculate a daily pancreatic protein output of 10 to 30 Gm. assuming an average enzyme concentration of 1 to 2 Gm. per 100 ml. (Hansson, 1959) in 1 to 1½ litres of exocrine secretion daily. It is this large protein synthesising capacity which results in the "concentration" of ^{75}Se - selenomethionine by the pancreas.

ii) Suitability of ^{75}Se - Selenomethionine as a Scanning Agent

Blau and Manske (1961) were the first to suggest that ^{75}Se - selenomethionine may be a suitable agent for pancreatic scanning when they found a consistently high level of localization in the dog pancreas after intravenous administration. The highest quantities were found 1 to 2 hours after administration and averaged about 6% of the injected dose. None of the elements in the structure of amino-acids (C, N, H, O and S) have gamma- emitting isotopes with half-lives longer than a few minutes. Since external measurements can only be done with gamma radiation, an amino acid derivative or analogue containing such an isotope must be used. As the selenium isotope ^{75}Se has the physical characteristics suitable for scanning (Chapter 2), ^{75}Se - selenomethionine can be used as a scanning agent.

iii) The Metabolism of Selenomethionine

In 1957, Cowie and Cohen demonstrated that selenomethionine could completely replace methionine for the normal exponential growth of a methionine requiring mutant of Escherichia coli. This result was of particular significance because it demonstrated that proteins in which methionine is replaced by its selenium analogue, retained their functional integrity. In vitro studies by Mudd and Cantoni (1957) showed that the substitution of the sulphur of methionine by selenium did not affect the activation of selenomethionine to Se - adenosyl - L - selenomethionine by the methionine activating enzyme and adenosine triphosphate. They also demonstrated that the Se - adenosyl derivative of selenomethionine could act as the direct donor of its methyl group to a suitable acceptor, thus retaining one of the most important biological functions of methionine.

Evidence of chemical similarity in a more complex biological system was provided by Spencer and Blau (1962) who demonstrated that ^{75}Se - selenomethionine accumulated identically with ^{35}S - methionine across everted hampster intestinal sacs in the presence of carrier methionine. McConnell and Cho (1961)[5] suggested, on the basis of their own data, that selenomethionine and methionine are probably absorbed from the intestine by a common transport system.

Studies by Hansson and Blau (1963) confirmed that selenomethionine may be utilized in mammalian protein synthesis. These authors injected ^{75}Se - selenomethionine into a pancreatic fistula cat. On hydrolysis and subsequent chromatography of the protein in the pancreatic juice they showed that 85% of the initial radioactivity in the juice appeared in a single peak at the position of selenomethionine. The incorporation of ^{75}Se - selenomethionine into human plasma proteins and haemoglobin has also been studied (Olendorf and Kitano, 1964; Penner, 1964; Awwad, Potchen, Adelstein and

Dealy, 1967). The available evidence demonstrates conclusively that ^{75}Se - selenomethionine may be utilised for protein synthesis in mammals.

iv) Potential Hazards in the Use of ^{75}Se - Selenomethionine

a) Radiation Dosimetry

Estimates of the dosimetry of ^{75}Se - selenomethionine in man are based on the data of Blau (1964). He suggested that the principal initial localization of the isotope is in the pancreas (7%) and in the liver (10%). The pancreatic uptake is utilized principally for the synthesis of digestive enzymes which are usually rapidly secreted, digested and then reabsorbed. Similarly, the liver uptake is principally into plasma proteins being synthesized at the time of injection. These then enter the general circulation. Blau considered that following the initial distribution there is extensive recycling of the isotope so that after the first day distribution is considered as essentially whole-body. His data is tabulated in Table 3.2 :-

Table 3.3

Selenomethionine: Biological Data (Blau, 1964)

Organ	Percentage of Administered Dose	Half-Life
Pancreas	7	4 hours
Liver	10	24 hours
Whole - Body	100	100 days

The gamma-ray constant for ^{75}Se, calculated for the 7 gamma-ray energies with abundance above 0.5% is 1.56r/mC - hr. at 1 cm.. In addition the short range radiation from x-rays and conversion electrons has been estimated at 0.0105 mev per ^{75}Se disintegration. Using these physical and biological factors the following integrated doses were calculated by Blau based on a routine scanning dose of 3 μ Ci/Kgm.:-

Total body dose	= 1.3 r
Extra dose to pancreas	= 0.06 r
Extra dose to liver	= 0.05 r
Highest total body dose rate	= 0.11 r/week

The maximum permissable radiation in man, though uncertain, is considered by Behrens and King (1964) to be less than 0.3 r per week. In a recent review of ^{75}Se - selenomethionine dosimetry in man, Numerof (1966) quotes Blau's estimations as being the most realistic published as other authors (Zuidema, Kirsh, Turcotte, Gaisford, Powers, Kowalczyk, 1964; Sodee, 1965) have based their estimations on animal data. The problem related to the extrapolation of data obtained from animals to man, is apparent when considering that the biological half-life of ^{75}Se - selenomethionine has been reported as ranging from 5 to 20 days in mice (Anghileri and Marques, 1965; Blau, Manske and Bender, 1962), 23 to 67days in dogs (Digiulio and Beierwaltes, 1964; Sodee, 1965) and 273 days in rhesus monkeys (Zuidema, Kirsh, Turcotte, Gaisford, Powers, Kowalczyk, 1964). Preliminary estimations in man have ranged from 36 to 144 days (Sodee, 1964; Penner, 1964). Ben-Porath, Case and Kaplan (1968) using normal human volunteer subjects calculated a whole-body radiation dose of 1.63 r for a tracer dose of 250 μCi in a 70 Kgm. man. This appears to be the most comprehensive study to date and agrees fairly well with Blau's estimations.

On the basis of Blau's (1964) data permission was granted by the Medical Research Council to administer 3 μCi/Kgm. ^{75}Se - selenomethionine to adult patients. Pregnant women and children were excluded from the study.

b) Toxicity of Selenomethionine

Toxicity due to inorganic selenium or the selenoamino acids has not yet been reported in man (Glover, 1968)**

Klug, Moxon, Petersen and Painter (1953) injected rats intraperitoneally with the selenoamino acids to determine the toxicity of these compounds. They calculated the DLso in rats to be 4.5 ($\pm$ 0.3)mg. selenium (selenomethionine) per Kgm. body weight. In man this would represent at least 3,200 times the quantity administered for scanning purposes.

Administration of methionine is purported to be dangerous in advanced liver disease (Watson, 1949; Kinsell, Harper, Giese, Margen, McCallie and Hess, 1949). However the adverse effects of methionine in patients with advanced liver disease became apparent only after oral administration of 8 to 20 grams. This is 32,000 times the tracer quantities of selenomethionine administered in this study. In addition symptoms of portosystemic encephalopathy are far more difficult to produce with intravenous administration of even large doses of methionine (Phear, Rhebner, Sherlock and Summerskill, 1956).

No adverse symptoms or signs developed in any patient in this study after selenomethionine injection.

** Personal Communication: Dr.J.R.Glover, Senior Lecturer in the Department of Social and Occupational Medicine, Welsh National School of Medicine, Cardiff.

Part 1. Aims of the Study

The two main aims of this study were:-

i) To define the normal and the abnormal pancreatic scan; and

ii) on the basis of this experience , to assess as objectively as possible the diagnostic accuracy of scan reporting.

The initial assessment of the normal and abnormal scan was based on a study of the first 160 patients of the total series of 200. The scans were viewed with a knowledge of the clinical details and investigation results in each patient. To assess the diagnostic accuracy of the scan reporting the last 40 consecutive scans of the series were viewed without knowledge of any clinical detail. To avoid bias which could result from seeing the patient, the patient selection and scan supervision was attended to by a colleague.

Part 2. Clinical Material

The clinical diagnosis of the 200 patients in this study are tabulated in Table 3.3

a) Classification

The patients have been classified into 3 main groups:-

Group1: Normal Pancreas

These patients were referred for a pancreatic scan to try and exclude occult pancreatic disease, particularly carcinoma. Many of the patients in this group suffered from anxiety states or depression with vague symptoms referable to the upper abdomen and weight loss. A number of patients with unexplained venous thrombosis and pyrexia of uncertain origin are included in this group.

Group 2: Pancreatic Disease

This group included patients suffering from a variety of disease states directly involving the pancreas. Patients suffering from systemic disease with definite pancreatic involvement such as diabetes mellitus, fibrocystic disease and from amyloidosis were included.

Group 3: Extrapancreatic Disease

This group was comprised of patients either suffering from a disease state commonly considered in the differential diagnosis of pancreatic disease eg. - cholelithiasis or obstructive jaundice, or from a condition which was likely to influence pancreatic function eg. - gastroenterostomy or vagotomy.

TABLE 3.3

TABULATION OF THE 200 PATIENTS SCANNED WITH ^{75}Se - SELENOMETHIONINE

ACCORDING TO CLINICAL DIAGNOSIS

CLINICAL DIAGNOSIS	NUMBER
1. NORMAL	67
2. PANCREATIC DISEASE	
a) Carcinoma	
i) Primary	13
ii) Ampullary	4
iii) Metastatic	1
iv) Islet Cell (Zollinger-Ellison Syndrome)	1
b) Pancreatitis	
i) Acute	18
ii) Chronic	15
c) Pseudopancreatic Cyst	2
d) Diabetes Mellitus	11
e) Partial Pancreatectomy	6
f) Fibrocystic Disease	1
g) Amyloid Disease	1
Total	73
3. EXTRAPANCREATIC DISEASE	
a) Intrahepatic Cholestasis	5
b) Bile - Duct Carcinoma	5
c) Cholelithiasis	12
d) Peptic Ulcer	14
e) Gastrectomy, Gastroenterostomy and Vagotomy	11
f) Aortic Aneurysm	2
g) Sarcoidosis	4
h) Gardner's Syndrome	1
i) Miscellaneous	6
Total	60

b) Diagnostic Assessment

The picture presented by the pancreatic scan would be most accurately confirmed by inspecting the pancreas in situ. For this reason in the initial assessment of the normal and abnormal pancreatic scan, the selection of patients for scanning was influenced by whether or not they were likely to come to laparotomy anyway. Operative or autopsy confirmation of the state of the pancreas was obtained in 105 (58%) cases. The breakdown of the diagnostic categories is presented in Table 3.4. This permitted an exact assessment of the position of the pancreas, the presence or absence of pancreatic pathology and the degree of hepatic - pancreatic overlap, in the majority of cases. In addition, the pancreas was assessed clinically; by relevant biochemical tests such as the glucose tolerance test, faecal fat estimation and secretion stimulation with duodenal aspiration; and by radiological procedures such as barium meal or selective coeliac arteriography. The tests performed varied from case to case. This study covers a two and a half year period and the majority of patients have been followed up clinically over this time. Therefore it is felt that the overall assessment of the presence or absence of significant pancreatic disease is probably accurate.

1. The Normal Pancreas

The pancreas was inspected at operation in 29 of 67 patients. In the remaining 38 patients a variety of tests including serum amylase, faecal fat and glucose tolerance test estimations were performed to help exclude pancreatic disease.

TABLE 3.4

DIRECT VISUAL CONFIRMATION OF PANCREATIC STATE

DIAGNOSIS	VISUALLY CONFIRMED	GROUP TOTAL
1. NORMAL	29	67
2. PANCREATIC DISEASE		
Carcinoma (All kinds)	19	19
Pancreatitis		
Acute	9	18
Chronic	7	15
Pseudopancreatic Cyst	0	2
Diabetes Mellitus	1	11
Pancreatectomy	6	6
Fibrocystic Disease	1	1
Amyloid	1	1
3. EXTRAPANCREATIC DISEASE		
Intrahepatic Cholestasis	0	5
Bile-Duct Carcinoma	5	5
Cholelithiasis	10	12
Peptic Ulcer	2	14
Gastroenterostomy	11	11
Aortic Aneurysm	2	2
Gardner's Syndrome	1	1
Sarcoidosis	0	4
Miscellaneous	0	6
Totals	104	200

2. Pancreatic Disease

Carcinoma of the Pancreas

In all 19 patients of this group the diagnosis was established by operative biopsy or resection.

Acute Pancreatitis

All 18 patients in this group had suffered at least one attack of acute pancreatitis from 1 week to 9 months prior to scanning. In 9 patients the diagnosis was confirmed at the time of the acute attack at laparotomy. In the others the diagnosis was made on the clinical picture and the raised serum amylase level.

Chronic Pancreatitis

Seven of the 15 patients in this group had operative confirmation of an indurated and diseased pancreas. In all 15 patients it was possible to elicit a history of previous abdominal pain and in all patients either radiological calcification or evidence of exocrine insufficiency on function testing or both, were present.

Pseudopancreatic Cyst

Two patients with pseudopancreatic cysts had the diagnosis confirmed by barium meal examination.

Diabetes Mellitus

There are 11 patients in this group. None of the patients had any clinical evidence of underlying primary pancreatic disease. All 11 patients in this group required medication either orally or systemically to control the blood sugar level. In 1 patient in this group, the pancreas was examined at laparotomy.

Pancreatectomy

The state of the pancreatic remnant as assessed at the time of operation was normal in 3 patients and involved by chronic pancreatitis in the other 3.

Fibrocystic Disease of the Pancreas

This patient, a girl of 16 years died 4 months after the scan. At autopsy, a pancreas of nearly normal size was found to be virtually replaced by fibro-fatty tissue. This patient also had classical pulmonary and hepatic involvement with portal hypertension. (Page 207)

Primary Amyloidosis

This patient suffered from extensive neurological involvement by primary amyloidosis. At autopsy 8 months after the scan the pancreatic parenchyma was extensively infiltrated with amyloid deposits. However the faecal fat content and glucose tolerance estimation were within normal limits. (Page 208).

3. Extrapancreatic Disease

Obstructive Jaundice

There were 10 patients in this group. All 5 patients suffering from carcinoma of the bile-duct underwent operation. The other 5 patients were suffering from cholestatic jaundice due to a variety of causes such as primary biliary cirrhosis, drug hepatitis, and infectious hepatitis. The primary hepatic cause for the cholestasis in these patients was confirmed by liver biopsy and liver function tests.

Cholelithiasis

Of 12 patients with cholelithiasis who were scanned, 10 underwent operation for cholecystectomy. In none of thes e patients was pancreatitis suggested clinically or biochemically.

Peptic Ulcer

This group consisted of 14 patients with symptomatic gastric or duodenal ulcers, all of which had been proven on barium meal. There was no clinical evidence of pancreatic disease in any of these patients. In 2 patients the presence of complications was confirmed at operation.

Postgastrectomy, Gastroenterostomy and Vagotomy

In all 11 patients in this group the pancreas was thought to be normal at operation.

Aortic Aneurysm

Two patients had upper abdominal aortic aneurysms confirmed at laparotomy.

Gardner's Syndrome

This patient a 36 year old woman presented the classical features of Gardner's Syndrome (Gardner and Richards, 1953) clinically with multiple polyposis coli and duodeni, osteomas of the maxilla, sebaceous cysts and a large fibrotic mesenteric mass confirmed at laparotomy. She was unusual in that there was no family history of polyposis coli.

Sarcoidosis

Of the 4 patients in this group, 3 had parotid involvement and a positive Kveim test. There was no clinical history of pancreatic disease and in all 4 patients the serum calcium was normal.

Miscellaneous

The 6 patients in this group suffered from hypothyroidism, acromegaly, hyperparathyroidism (2 patients) primary hyperlipidemia and coeliac disease. In none of this group was there clinical evidence of pancreatic disease.

Part 3. Technique of Pancreatic Scanning

Fig.3.2: Patient in position for a pancreatic scan. Cassette above the control panel contains the film for the photoscan. Colour scan is produced on a platform to the right of the scanner (outside picture). Page 73 .

i) Scanning Machine

The scans were performed with a 5" crystal Picker Magna Scanner (Picker X-Ray Corporation, New York) using an 85 hole collimator of nominal focal length 12 cm. and a scanning speed of 24 cm./minute. A photoscan (Fig.3.7) and coloured "scantiscan" (Fig.3.6) was obtained on each patient scanned. The details of the machine settings for ^{75}Se are given in Chapter 2.

ii) ^{75}Se - L - Selenomethionine

The ^{75}Se - L - selenomethionine was supplied by the Radiochemical Centre (Amersham) in aqueous solution which had been sterilized by autoclaving in accordance with the requirements of the British Pharmacopoeia.

The specific activity was 200 - 800 mc./mM. An excess of cysteamine hydrochloride (2 mgs./mCi) was added to each batch on arrival to act as an antioxidant (Blau, 1964).

To facilitate administration the 1mCi/ml. supplied was diluted to a volume of 10 ml. with 0.9% saline and stored in sterilized rubber-topped dark bottles.

iii) Patient Preparation

This subject is discussed in Chapter 5.

No special preparation was employed in most of the cases but the patients were encouraged to take as complete a diet as possible for the few days preceding the investigation and a large breakfast on the morning of the scan. The procedure was performed on both in- and out- patients.

iv) Procedure

A dose of 3μCi per kilogram of body weight was injected intravenously. In 6 patients the isotope was administered subcutaneously into the buttocks with 1200 u of hyaluronidase. The results were as satisfactory as after the conventional intravenous injection.

The position of the costal margin was marked on the skin and transposed as surface markings onto the paper used for recording the colour scan.

The pancreatic scan was begun 30 to 60 minutes after injection of the isotope.

Patients were scanned supine (Fig.3. 2) or with their head and shoulders slightly elevated for comfort. Scanning was usually commenced at a level just above the xiphisternum. The average duration of the scan was 40 to 50 minutes.

A ^{198}Au - colloid gold liver scan was performed in all patients for precise location of the liver edge. The scans were performed in this sequence as scattered radiation from the higher energy gamma radiation emitted by ^{198}Au interfered with the ^{75}Se counting (Fig.2. 3). The principles and dosimetry of ^{198}Au colloid - gold liver scanning are contained in Appendix 3.

v) The Timing of the Pancreatic Scan

The pancreatic scan was performed 30 to 60 minutes after the injection of the isotope. A second scan was performed in an initial group of patients between 2 to 6 hours after the injection but was subsequently abandoned as it rarely added further information.

Fig.3.3a: Normal pancreas. Scan commenced 30 minutes after isotope injection.

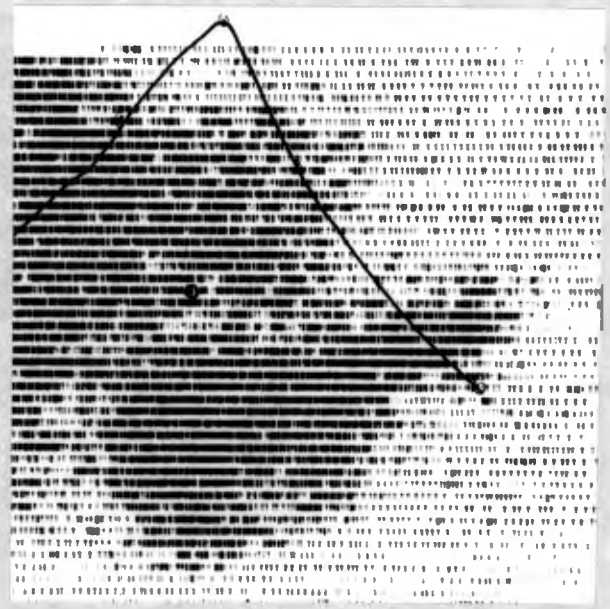

Fig.3.3b: Scan performed at 6 hours after isotope injection.

Early serial studies showed that the isotope label is distributed widely throughout the pancreatic parenchyma 30 minutes to 2 hours after the isotope injection (Fig. 3.3a). A scan performed at 6 hours, on identical machine settings in the same patient showed the activity to be concentrated toward the centre of the body of the pancreas and then toward the head (Fig.3.3b). This scan gave the erroneous impression of thinning in the tail of the pancreas. It was concluded that the optimum time for scanning would be when there was diffuse distribution of the isotope in the pancreas i.e. approximately 30 minutes to 2 hours after injection.

Part 4. Results

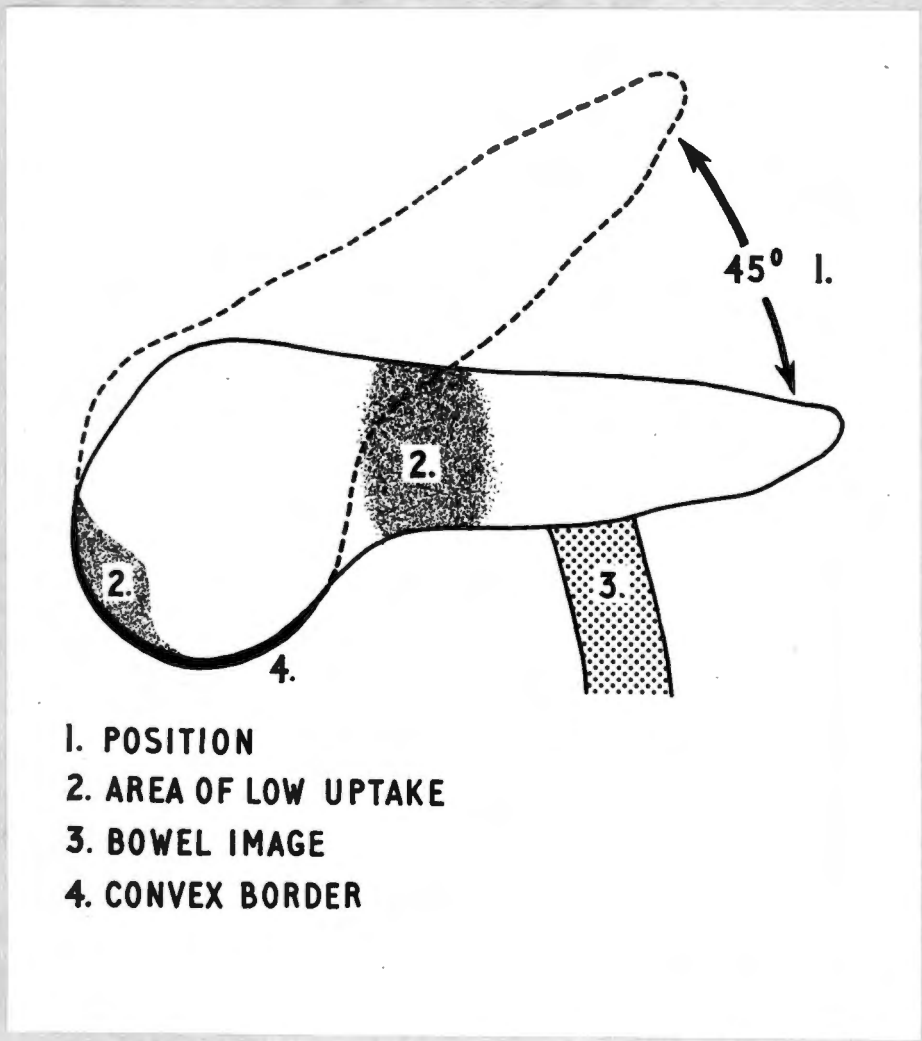

Fig.3.4: Diagrammatic representation of the main features of the normal pancreatic scan.

For the sake of clarity the case records of the patients whose scans are used to illustate features of the normal and abnormal scan are presented in Appendix 1.

An analysis of the reports of the pancreatic scans on the 200 patients in this study is presented in Table 3.5

A. The Normal Pancreas

The features of the normal ^{75}Se - selenomethionine pancreatic scan are illustrated diagrammatically in the line drawing (Fig.3.4).

i) Position

The most striking feature is the variation in the position of the body and tail in relation to the head. This varied from a horizontal position (Fig.3.5) to one lying approximately 45° (Fig.3.6 , 3.7).

ii) Shape

The shape of the gland varied between two common configurations; the neck, body and tail assumed either a straight line (Fig.3.6) or a sigmoid shape (Fig.3.5).

iii) Isotope Distribution within the Pancreas

A frequent finding is an area of decreased uptake in the vicinity of the neck of the gland (Fig.3.5). This gives the false impression of a filling defect. This appearance is presumed to be due to the adjacent portal vein compressing the pancreatic parenchyma. This particular feature should

TABLE 3.5

AN ANALYSIS OF THE REPORTS OF THE PANCREATIC SCANS ON THE 200 PATIENTS IN THIS STUDY

CLINICAL DIAGNOSIS	SCAN REPORTS			
	Normal	Abnormal	Unreadable	Total
1. NORMAL	57	4	6	67
2. PANCREATIC DISEASE				
a) Carcinoma				
i) Primary		10	3	13
ii) Ampullary	1	3		4
iii) Metastatic		1		1
iv) Islet Cell (Zollinger-Ellison Syndrome)		1		1
b) Pancreatitis				
i) Acute	7	9	2	18
ii) Chronic	1	12	2	15
c) Pseudopancreatic Cyst		2		2
d) Diabetes Mellitus	4	6	1	11
e) Partial Pancreatectomy		6		6
f) Fibrocystic Disease		1		1
g) Amyloid Disease		1		1
			Total	73
3. EXTRAPANCREATIC DISEASE				
a) Intrahepatic Cholestasis	5			5
b) Bile-Duct Carcinoma	5			5
c) Cholelithiasis	8	4		12
d) Peptic Ulcer	11	3		14
e) Gastrectomy, Gastroenterostomy and Vagotomy	6	5		11
f) Aortic Aneurysm		2		2
g) Sarcoidosis	2	1	1	4
h) Gardner's Syndrome		1		1
i) Miscellaneous	6			6
			Total	60

Fig.3.5: (Patient 2): Photograph of a colour scan of a normal sigmoid-shaped pancreas with a prominent area of "physiological" thinning between the head and the body of the pancreas (shown as stippled area on the inset). The adjacent liver shadow is contiguous with, but does not overlap, the pancreas. The surface markings of the costal margins are indicated by the black lines.

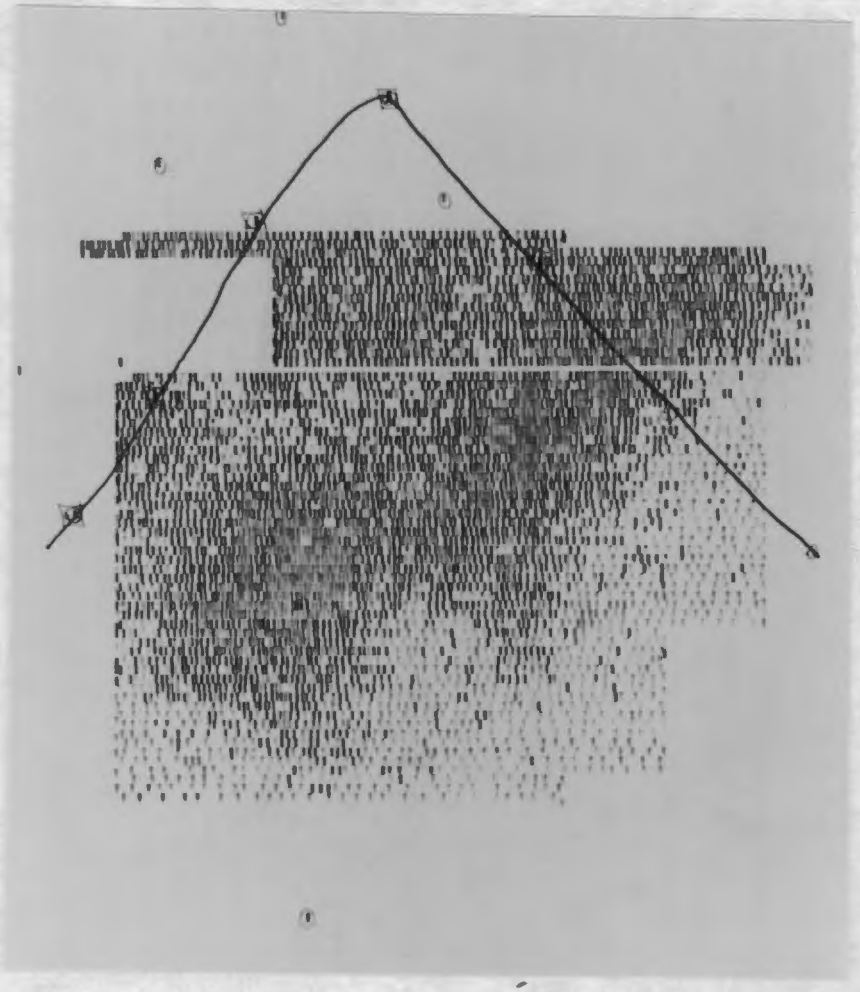

Fig.3.6.(Patient /): Colour scan of a normal pancreas. The surface markings of the costal margins are indicated by the black lines.

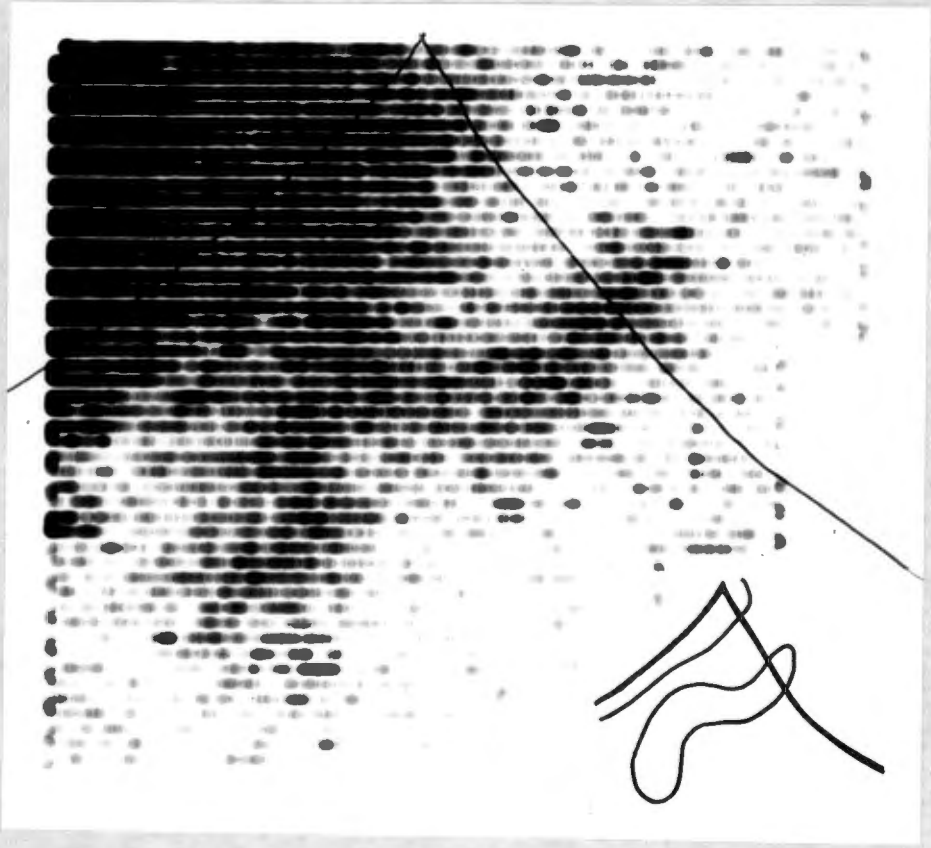

Fig.3.7: (Patient 4): Photoscan of a normal pancreas.

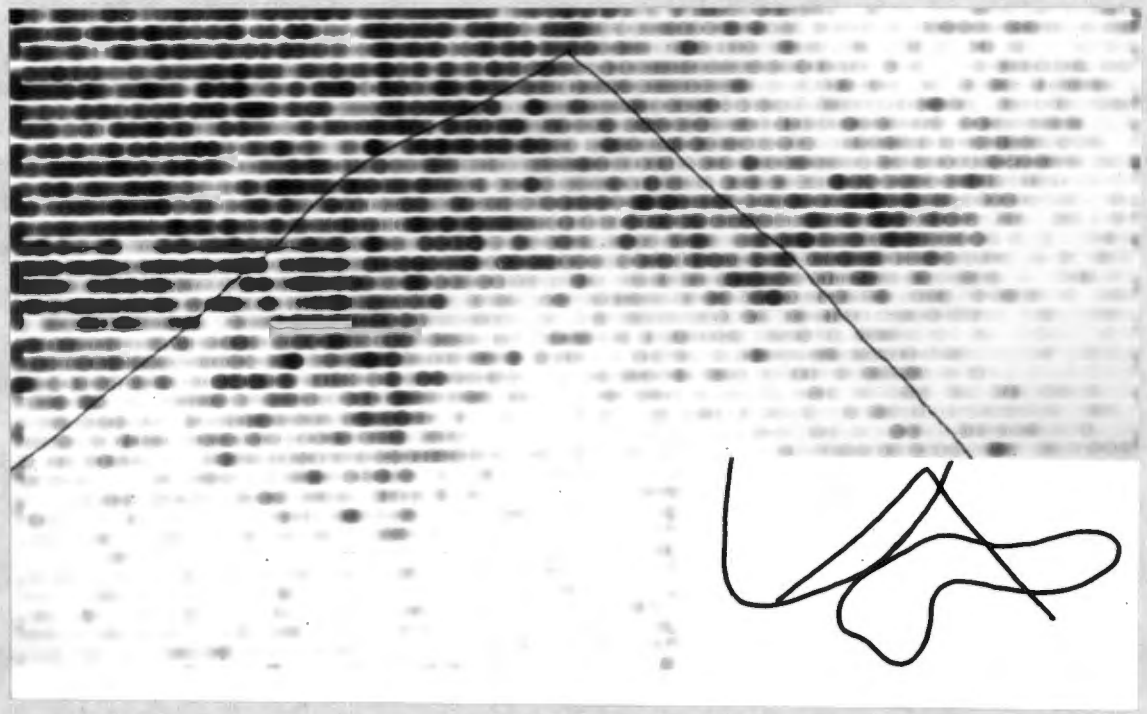

Fig.3.8: (Patient 3): Normal sigmoid - shaped pancreas with bifid head appearance.

be examined critically as pathology in this region may be overlooked. For example, Fig.3.21 . illustrates a pancreatic scan in which the area of "physiological thinning" is considerably enhanced without any displacement of the pancreas. This was associated with a fusiform aneurysm of the aorta posterior to the body of the pancreas. In Fig.3.24 there is a clear filling defect in the same area of the pancreatic scan. In this patient it was due to infarction of the pancreatic parenchyma following relapsing acute pancreatitis.

Another less common physiological filling defect is observed on the duodenal margin of the head and in the extreme cases this resulted in the head showing a distinct bifid appearance (Fig.3.8). There are two main factors which could produce this effect. One is the termination of the combined pancreatic and common bile-ducts and the other is uptake by the duodenal mucosa of the ^{75}Se - selenomethionine. It is likely that the importance of either of these factors varies from patient to patient.

iv) Uptake of ^{75}Se - Selenomethionine by Liver and Bowel

The most constant visceral uptake other than that of the pancreas is by the liver and proximal small bowel. Liver uptake is a universal feature and a subsequent liver scan is essential to determine the precise location of the liver edge especially in those cases in which it is contiguous with or overlaps the pancreas. Thirty six of the total 67 patients in this group had some degree of overlap of the pancreas by the liver. This usually involved less than 25% of the total pancreatic area. However in these cases the scan was considered normal as the overlapped area showed good reinforcement of the hepatic shadow. In particular there was no alteration in the normal position or contour of the pancreas. Although such a case has not yet been encountered, it is conceddd that a very small lesion in the overlapped area

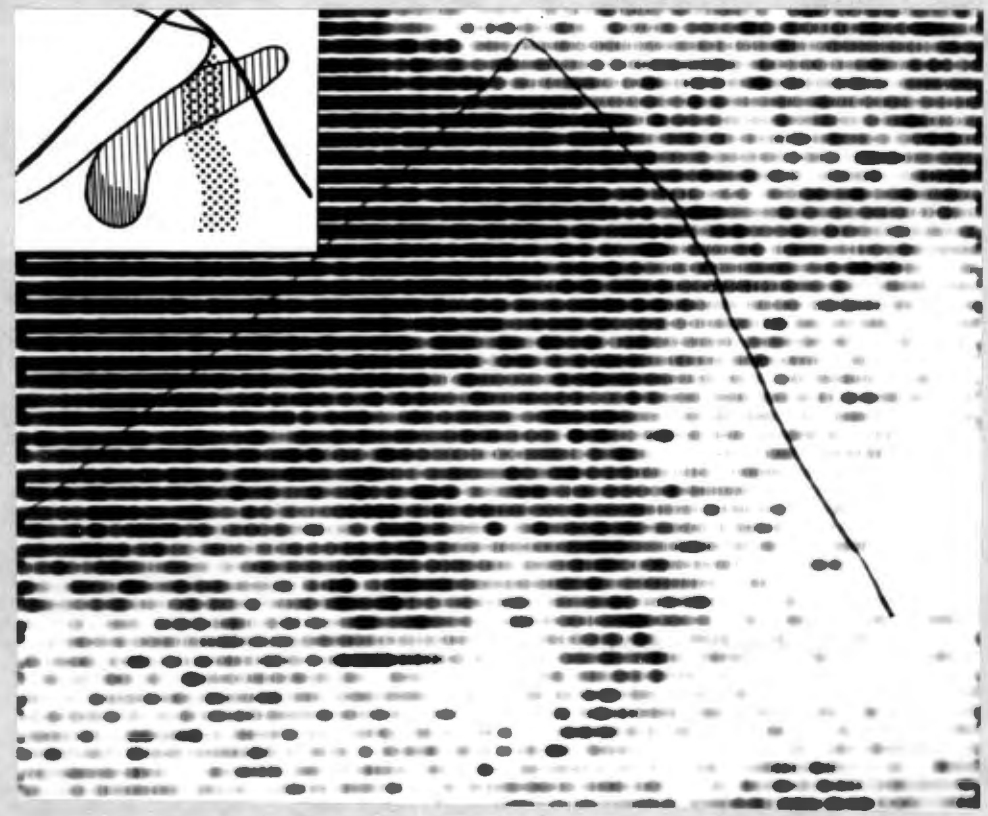

Fig.3.9:(Patient)4) Photoscan of a patient with diabetes mellitus. The considerable bowel uptake (the dotted area on the inset) and relatively lower activity in the tail of the pancreas convey the erroneous impression of a "horse-shoe" shaped pancreas.

could not be excluded.

In 13 (6.5%) scans of the whole series the pancreatic outline was obscured by uptake in the overlying liver. Unless hepatomegaly is gross it is not always possible to predict prior to scanning whether the liver uptake will interfere with the pancreatic scan. In the event of overlap by the liver, the convex lower margin of the pancreas head is an important and useful landmark in assessing the pancreatic position (Fig.3.4). Provided there is uptake by the pancreas this convex margin invariably projected below the left lobe of the liver. The localization of the reinforced hepatic-pancreatic uptake can then be determined by its normal relationship to the head of the pancreas.

The usual position of visible bowel uptake is shown in Fig.3.4 . This localization is remarkably constant in relation to the lower margin of the body and tail of the pancreas and is presumed to be uptake of a fixed position of the bowel. This would correspond to the distal duodenum and proximal jejunum at the position of the ligament of Treitz. Uptake in this region is sometimes more impressive than in the pancreas and can give the false impression that the tail of the pancreas is deflected downwards (Fig.3.9).

Bilateral uptake of the ^{75}Se - selenomethionine which may be due to renal uptake or excretion that has never been recognised.

v) Reproducibility of Scans

The reproducibility of the main anatomical features described is good. Six normal patients and three patients with pancreatic disease and abnormal scans had their scans repeated after an interval of 6 to 12 months. In all the patients the main features of both scans were similar. However uptake of

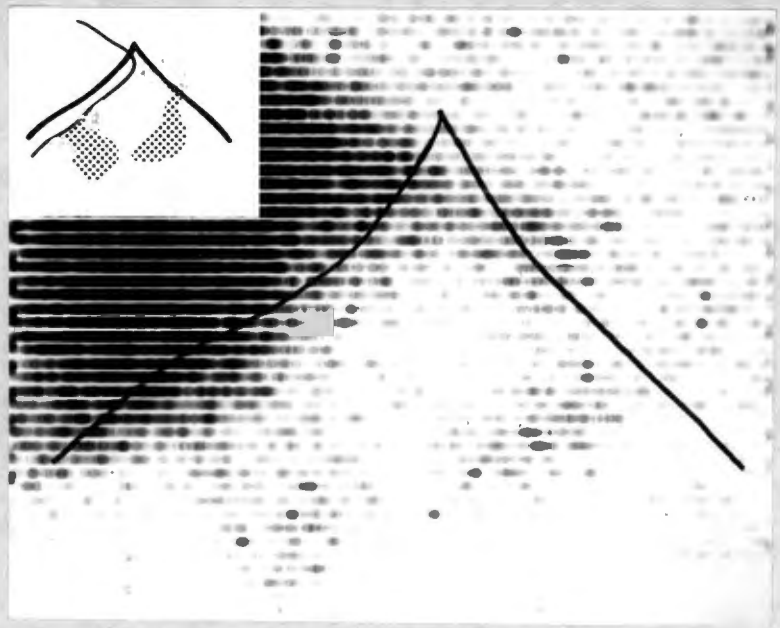

Fig.3.10a:(Patient 9): Photoscan of the pancreas 10 days after severe clinical attack of acute pancreatitis. Isotope uptake by the pancreas is severely impaired.

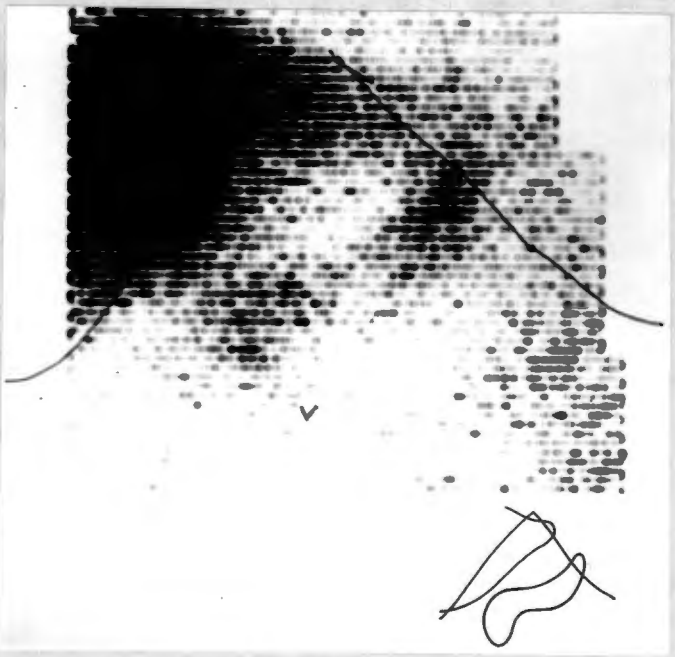

Fig.3.10b:(Patient 9): A repeat scan in the same patient 10 months later. Pancreatic uptake has improved considerably.

isotope in the organs did differ in relation to the functional state of the organ. For example, Fig.3.10a illustates the scan of a patient who had suffered a severe clinical attack of acute pancreatitis 10 days previously. Pancreatic uptake is considerably diminished. The patient was rescanned 10 months later after a full clinical recovery and no further attacks. Fig.3.10b shows the considerably increased pancreatic uptake in the same patient.

vi) Influence of Hepatic Function on the Scan

In 2 patients with active chronic ("lupoid") hepatitis and severely disordered liver function tests, the pancreatic uptake was partially obscured by the very high background activity. This was attributed to a failure by the liver to take up selenomethionine in the normal fashion.

vii) Failure of Uptake in the Normal Pancreas

Four patients in whom there was no evidence of pancreatic dysfunction had abnormal scans. All were over the age of 65 years. Two had diffuse atheroma of the aorta and its branches with splenic artery aneurysms on coeliac artery arteriography. One patient had thyrotoxicosis. In all patients there was diffuse failure of uptake of the isotope.

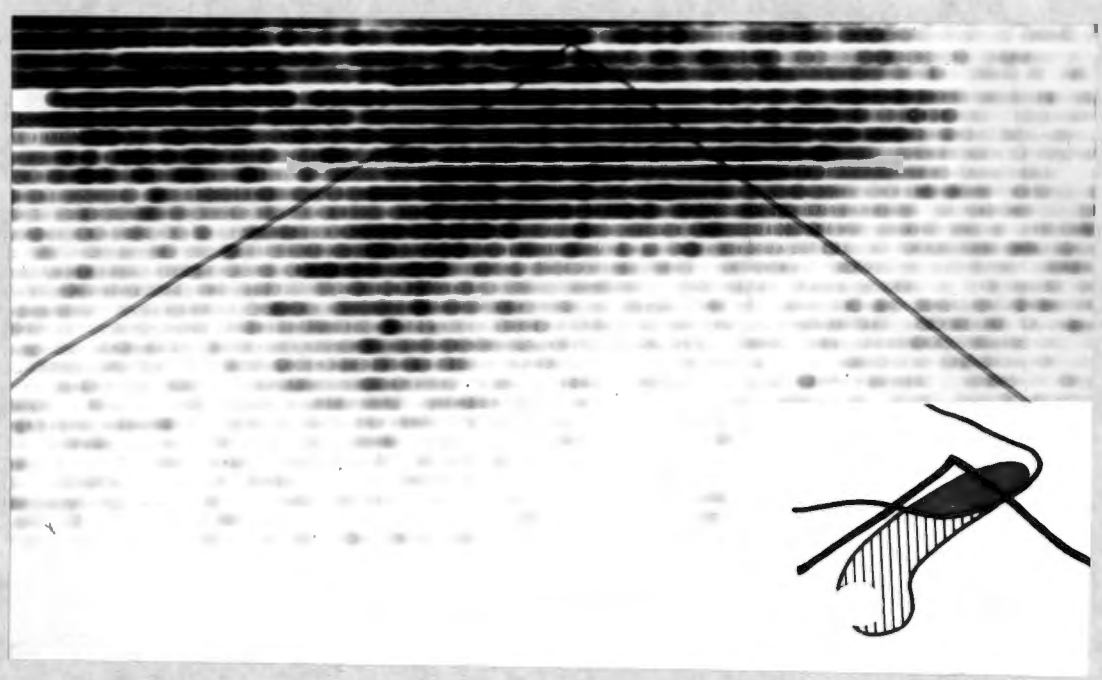

Fig.3.11:(Patient 5): Photoscan showing a circumscribed filling defect in the head of the pancreas. A 3 cm. diameter carcinoma in the head of the pancreas was found at operation.

B. The Abnormal Pancreas

1. Carcinoma

i) Primary Pancreatic Carcinoma

In 10 of the 13 cases in this group the scan was definitely abnormal. Three patients had a circumscribed filling defect on the scan (Fig.3.11). In 7 patients there was more diffuse failure of isotope uptake. This was due to co-existant pancreatitis in 2 in whom there was failure of uptake well beyond the limits of the tumour. In the remaining patients isotope uptake was diffusely poor in part or the whole of the gland depending on the degree of infiltration (Fig.3.12).

With an expanding lesion the adjacent normal tissue was invariably displaced and distorted (Fig.3.13). However there was seldom complete absence of uptake in the area occupied by the tumour.

Three patients had hepatomegaly with the pancreas completely obscured. The scan was of very limited value in these cases.

ii) Carcinoma of the Ampulla of Vater

Three out of 4 patients showed diffusely poor uptake of the isotopic label by the pancreas. The other patient had a normal scan.

iii) Functioning of Islet-Cell Tumour

In one case of the Zollinger - Ellison Syndrome in which the patient suffered recurrent bouts of abdominal pain attributed to relapsing pancreatitis, the pancreatic scan shows very poor uptake in the head and neck but excellent

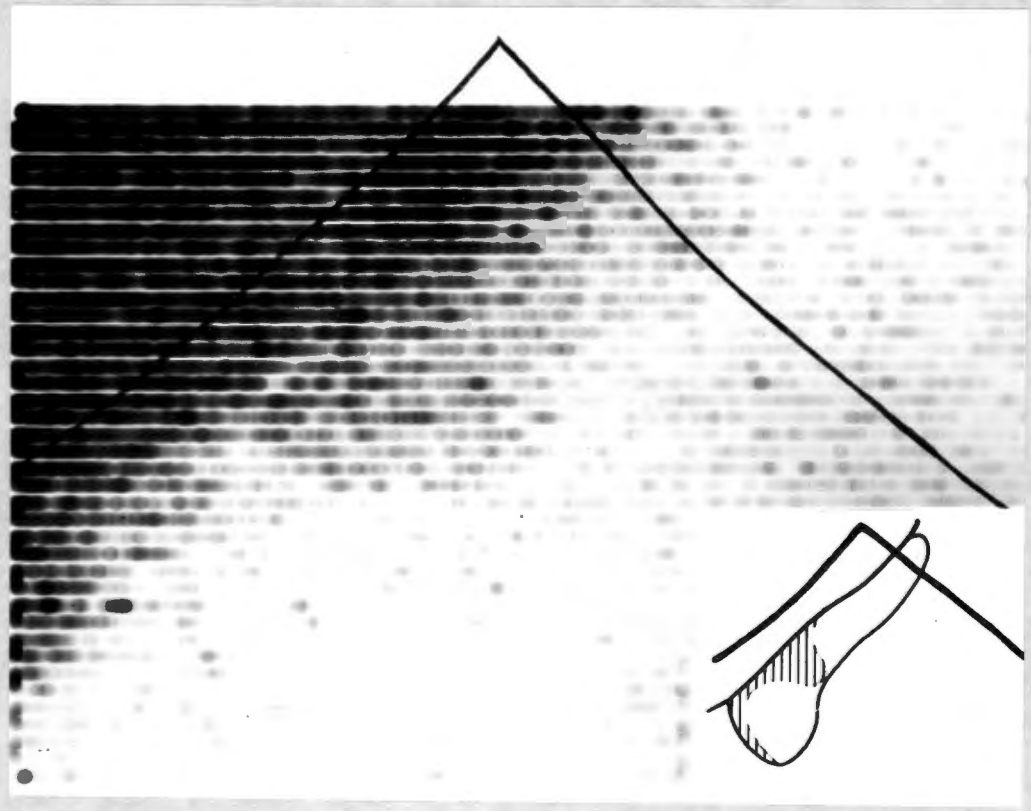

Fig.3.12:(Patient 6): Photoscan of a patient with carcinoma of the pancreas showing a filling defect of the head, body and tail of the pancreas. The hatched area on the inset represents the site of discernable isotope uptake by the pancreas.

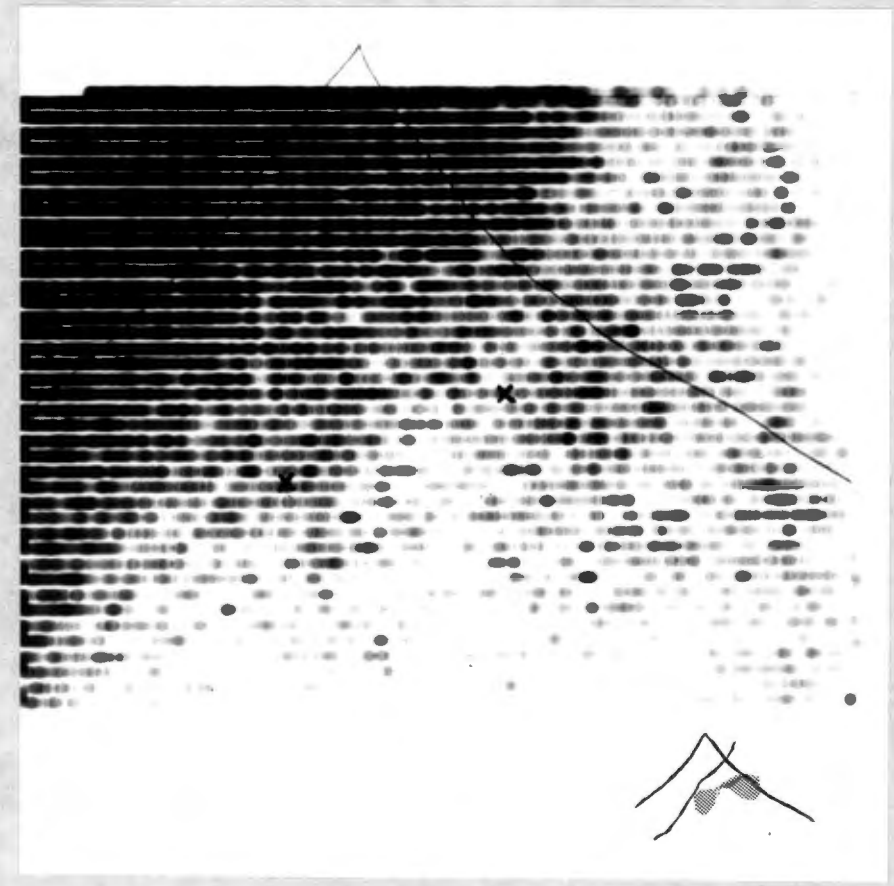

Fig.3.13: (Patient 7): Photoscan of a patient with carcinoma of the body of the pancreas. The normal pancreatic configuration is disrupted by the growth with considerable displacement and distortion of the pancreatic parenchyma. The two crosses represent the surface markings of the lateral limits of the palpable epigastric mass. These approximate well to the limits of the filling defect on the scan.

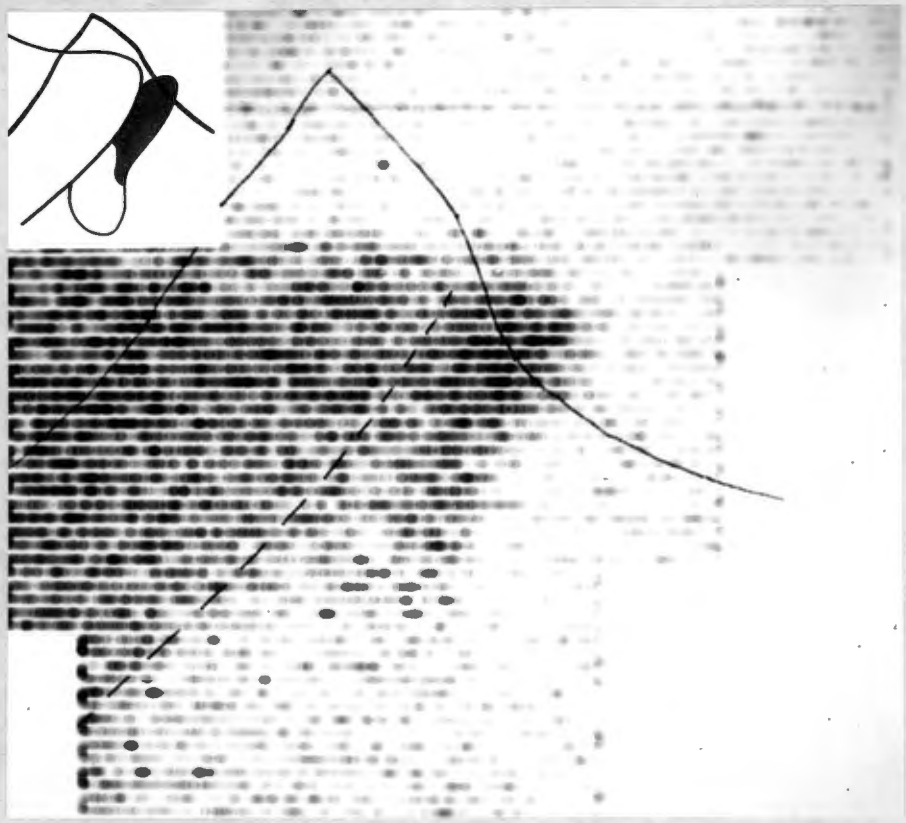

Fig.3.14a(Patient 8): Photoscan of a patient with chronic pancreatitis and a functioning α-cell carcinoma in the tail of the pancreas. The black area on the inset represents the site of the tumour. There is failure of isotope uptake by the head, neck and part of the body of the gland. The broken line represents the liver margin.

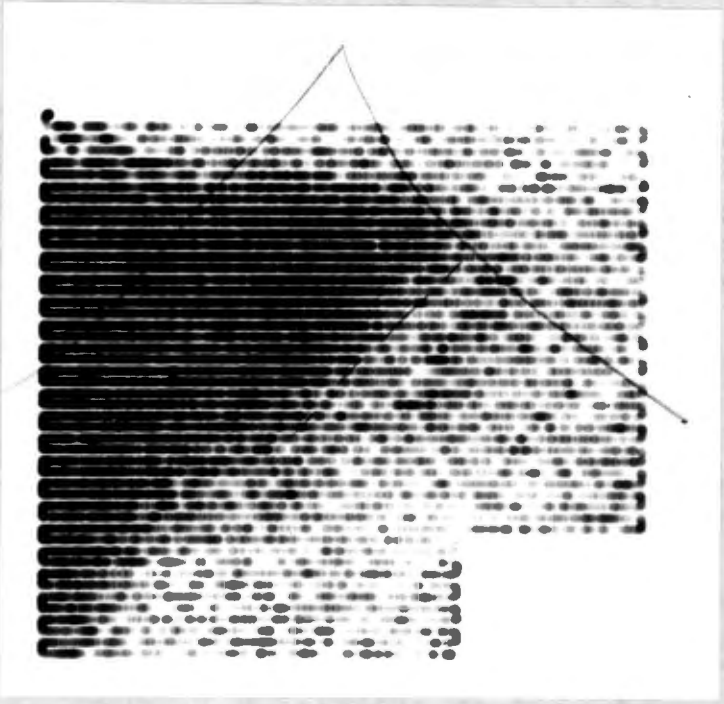

Fig.3.14b:(Patient 8): A scan performed 3 months after a distal pancreatectomy in the patient suffering from the Zollinger-Ellison Syndrome (Fig.3.14a.). The area of pancreatic uptake is absent.

uptake in the tail (Fig.3.14a). Because the scan density was greater at this point than in the middle of the right lobe of the liver, normally some 6 to 8 cms. thicker, it was interpreted as representing enhanced uptake of the selenomethionine by the tumour tissue. At laparotomy the head, neck and tail of the pancreas were fibrosed and indurated because of the co-existant pancreatitis. The site of maximum uptake in the tail of the pancreas coincides with the position of an infiltrating poorly differentiated α - cell carcinoma of the islets. Distal two-thirds pancreatectomy was associated with loss of the "hot" area on a scan repeated 4 months post-operatively (Fig.3,14b).

iv) Metastatic Carcinoma of the Pancreas

A scan showing the tail of the pancreas slightly expanded was seen in a patient with metastatic carcinoma of the pancreas. Biopsy of the pancreas at laparotomy showed extensive secondary adenocarcinomatous involvement of the pancreatic lymphatics. The primary site was an adenocarcinoma of the sigmoid colon. Extensive malignant involvement of the tail of the pancreas had displaced the functioning parenchyma to give a broadened appearance.

2. Pancreatitis

i) Acute Pancreatitis

Of the 18 patients in this group, 9 had abnormal scans. The features are failure of isotope uptake in part (Fig.3.15) or the whole (Fig.3.10a) of the pancreas. Changes are generally more apparent in the head than the tail of the pancreas. All these 9 patients with abnormal scans had active pancreatic disease at the time of the scan with the classical pain and tenderness and raised serum amylase. The abnormal pancreatic scan was apparent for 2 to 3 weeks after the acute attack.

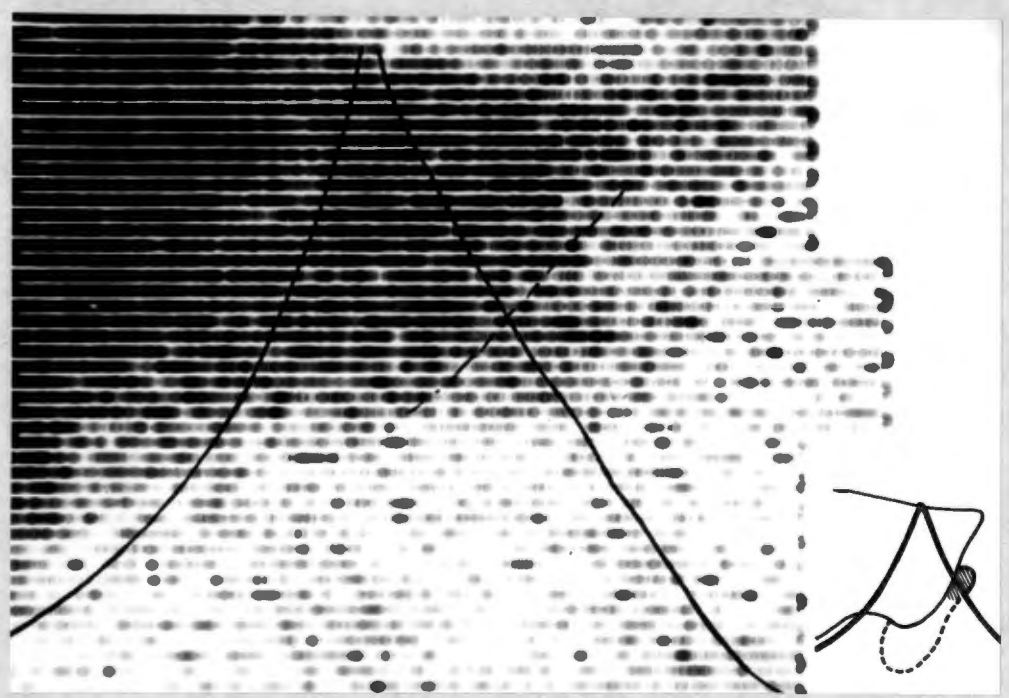

Fig.3.15:(Patient *10*): Photoscan of a patient with acute pancreatitis. There is diffuse failure of isotope uptake in the gland with the exception of a small area in the tail (the cross-hatching on the inset). The broken line indicates the outer margin of the left lobe of the liver.

In 7 patients the scan was normal. Significantly, at the time of study all of these patients were in clinical remission. The scan was performed within 3 to 36 weeks after a documented attack of pain.

Recovery of pancreatic function with restoration of the scan to normality is documented in Figs. 3.10a . and 3.10b . This patient was described on page. 89 . Liver overlap prevented the interpretation of the scan in 2 out of the 18 patients.

ii) Chronic Pancreatitis

In 12 of the 15 patients in this group the scan was abnormal with generalized failure of isotope uptake (Fig.3.16a). The diminution of isotope uptake can generally be related to the severity of the exocrine insufficiency.

In 1 patient with steatorrhoea the scan was within normal limits.

In 2 patients the scan was considered unreadable because of significant hepatomegaly.

3. Pseudopancreatic Cyst

Two patients with pseudopancreatic cysts had abnormal scans. The abnormality detected was an area of increased activity in relation to the body and tail of the pancreas (Fig.3.17). One patient developed the pseudocyst following an attack of acute pancreatitis. In the other, it arose as a result of surgical trauma to the pancreas at the time of splenectomy.

4. Diabetes Mellitus

In 6 of the 11 patients in this group the uptake was considered to be

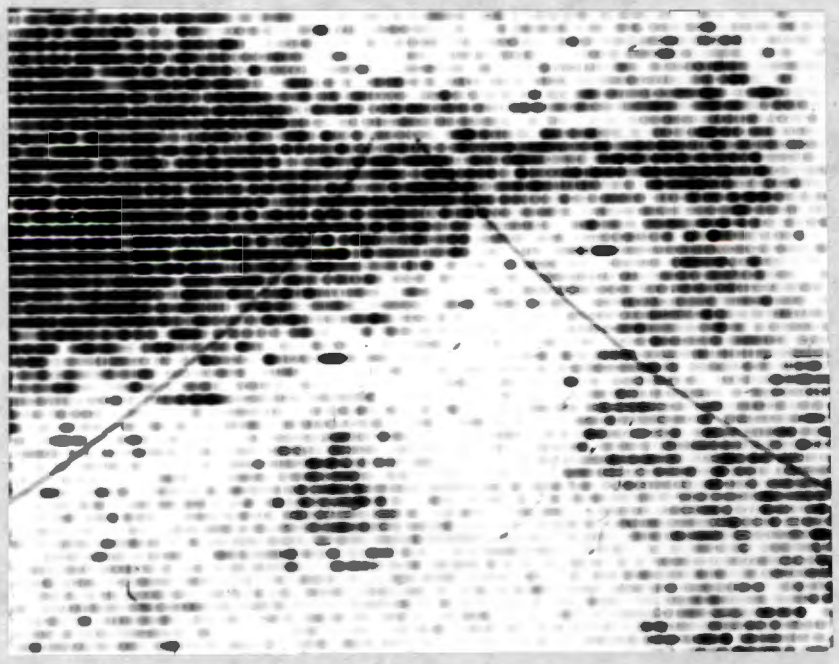

Fig.3.16a:(Patient 2) Photoscan of a patient with calcific pancreatitis (Fig.3.15b), associated with excessive ethanol consumption. The only pancreatic uptake discernible is an island of activity inferior to the left lobe of the liver. The isotope uptake on the right of the photograph is in bowel.

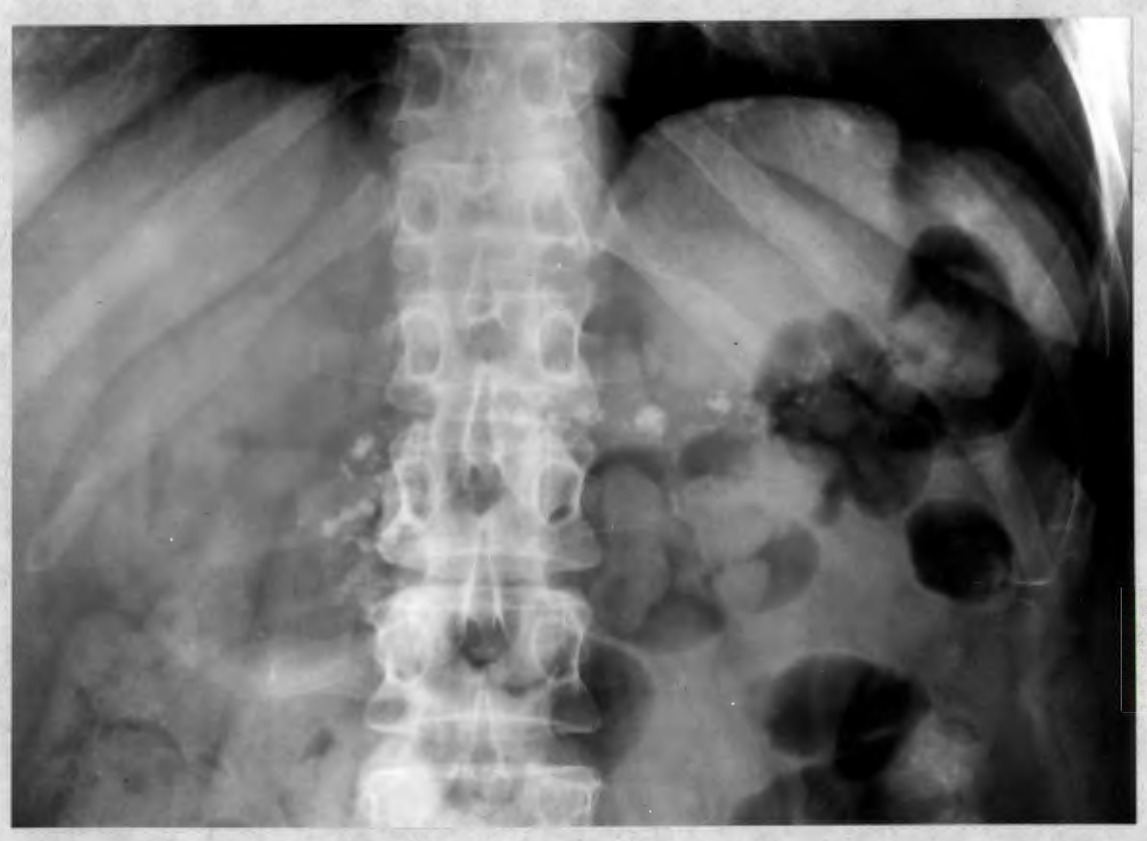

Fig.3.16b: Photograph of an abdominal x-ray in the patient in Fig.3.16a showing the pancreatic calcification.

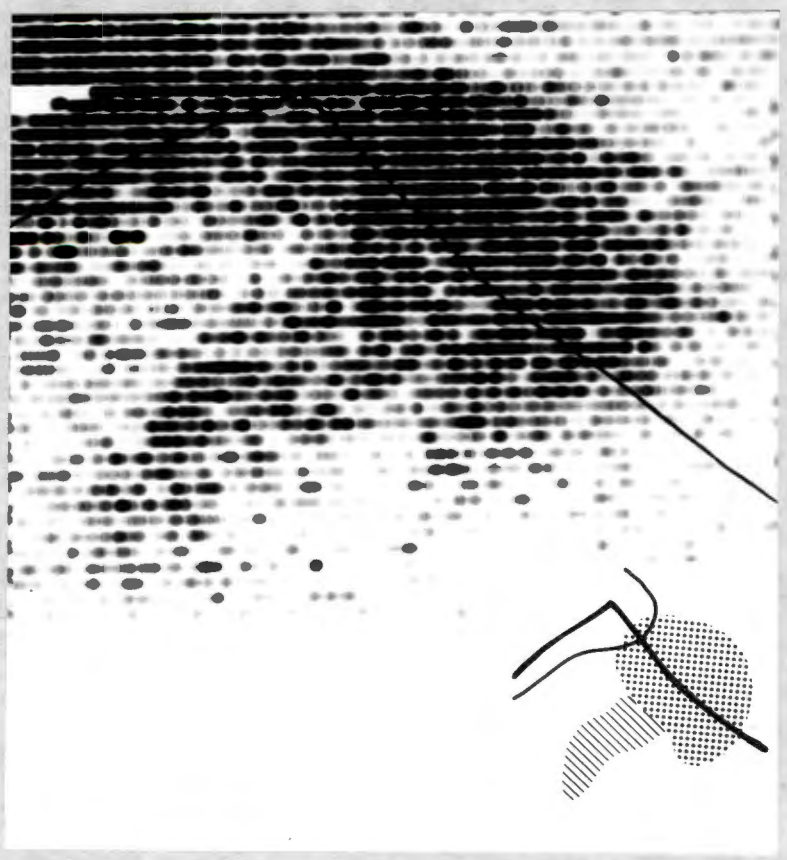

Fig.3.17:(Patient)Photoscan of a pseudopancreatic cyst showing an area of increased activity overriding the body and tail of the pancreas (stippling on inset). The liver is in the left hand corner and only just overlaps this active area. Uptake by the rest of the gland appears reduced.

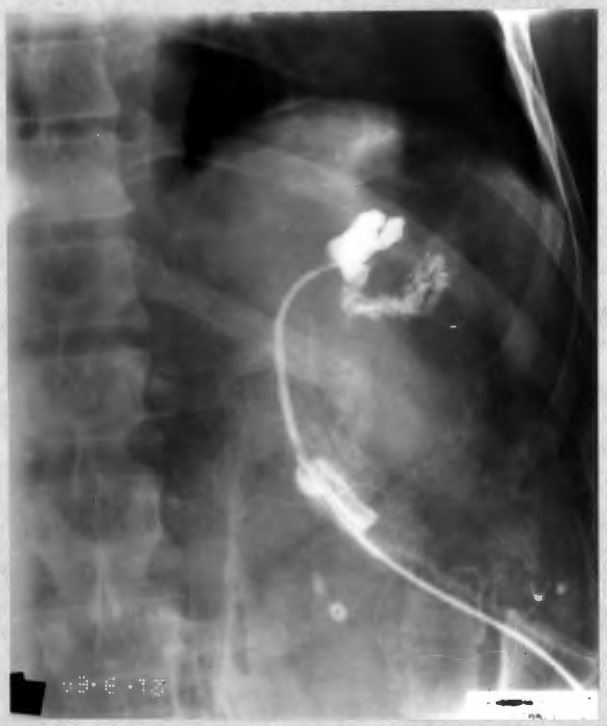

Fig.3.18a: Dye passed through a catheter placed in a pancreatic fistula in the patient depicted in Fig.3.16, pools behind the stomach.

Fig.3.18b: Barium meal in the same patient two weeks after the fistula had stopped draining shows a filling defect on the greater curvature of the stomach.

decreased. One patient, a very labile insulin dependent diabetic was examined at laparotomy and found to have a normal pancreas (Fig.3.9). The quality of the scan was generally poorer in insulin dependent diabetics.

One scan was considered unreadable because of the gross overlap.

5. Partial Pancreatectomy

Isotope uptake was poor in the pancreatic remnant of all 6 patients in this group.

6. Fibrocystic Disease of the Pancreas

The scan showed complete absence of uptake. This was so striking that the pancreas appeared as a filling defect against the normally low count rates of the adjacent intestine and enlarged spleen.

7. Primary Amyloidosis

Uptake was considerably reduced in this patient with advanced primary amyloidosis.

C. Extrapancreatic Diseases

i) Peptic Ulcer

Three out of 14 patients in this group showed abnormal scans. One patient with low pancreatic uptake was on nasogastric suction and probanthine for severe ulcer pain. Clinically the symptomatology was more typical of ulcer pain than pancreatitis and the serum amylase was normal. In the second patient the scan shows the tail of the pancreas to be displaced upwards under the liver edge (Fig.3.19). At operation this displacement was confirmed. It was due to contraction of fibrous scar tissue from a chronic gastric ulcer involving the tail of the pancreas. In the third patient the scan shows elongation, displacement and thinning of the neck of the pancreas (Fig.3.20). This patient had developed a subacute perforation of a duodenal ulcer with an inflammatory mass which had formed medial to and was displacing the neck of the pancreas. These changes were confirmed at laparotomy.

ii) Cholelithiasis

Four patients of the 12 in this group showed abnormal scans with decreased uptake of isotope. Three of these patients had abnormal induration of the pancreas at operation. The accent of the pathology was in the head of the pancreas.

iii) Aortic Aneurysms

Two patients had aortic aneurysms, confirmed at laparotomy, and abnormal scans. A filling defect in the mid-portion of the body of the pancreas in one patient was caused by compression by a fusiform aneurysm of the abdominal aorta (Fig.3.21). There is excellent pancreatic uptake and no displacement of gland tissue adjacent to the filling defect.

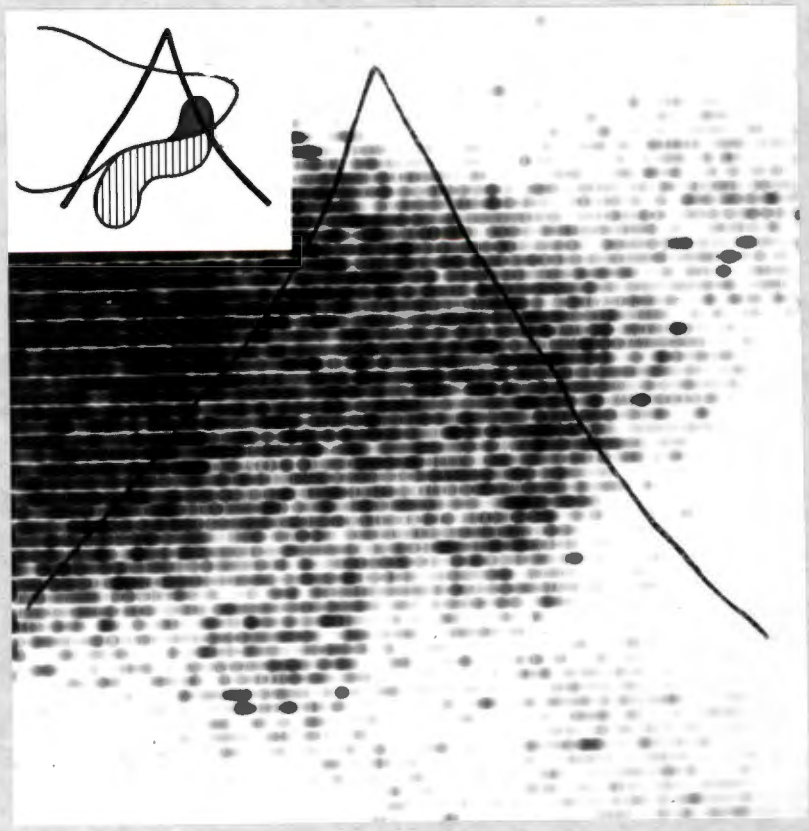

Fig.3.19:(Patient)6) Photoscan of a patient with a chronic perforating gastric ulcer in whom the tail of the pancreas was involved by fibrous scar tissue and displaced upwards under the left lobe of the liver.

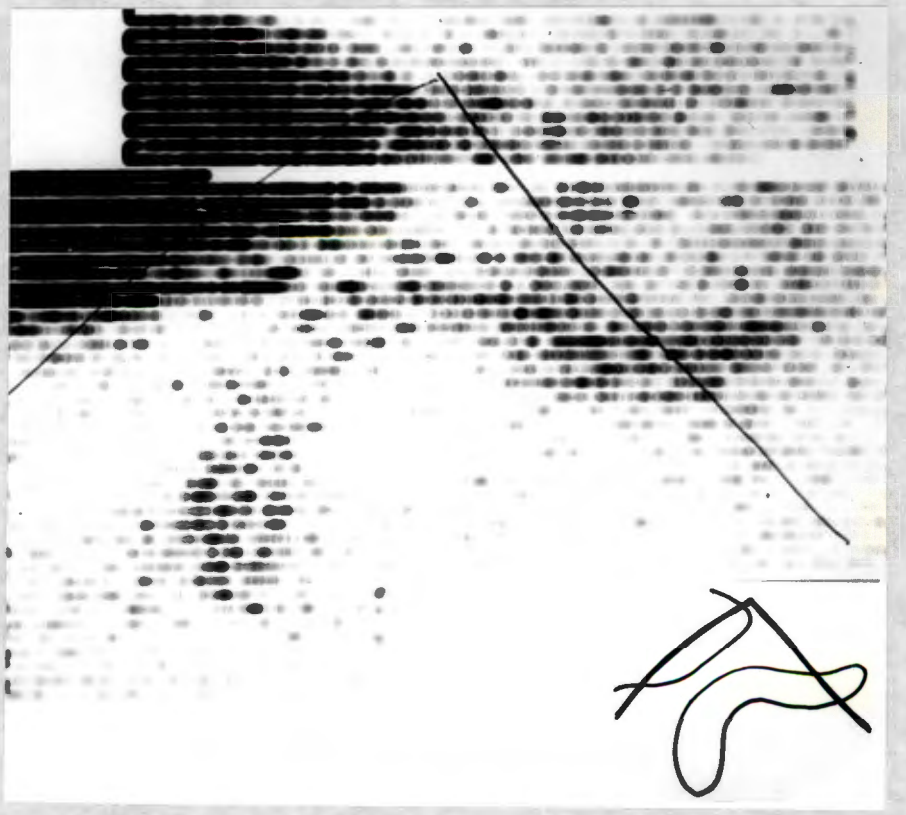

Fig.3.20:(Patient)(5) The head and neck of the pancreas are compressed and displaced laterally in this photoscan by a mass medial to the head of the pancreas. This was an omental mass which formed in relation to a subacute perforation of a duodenal ulcer.

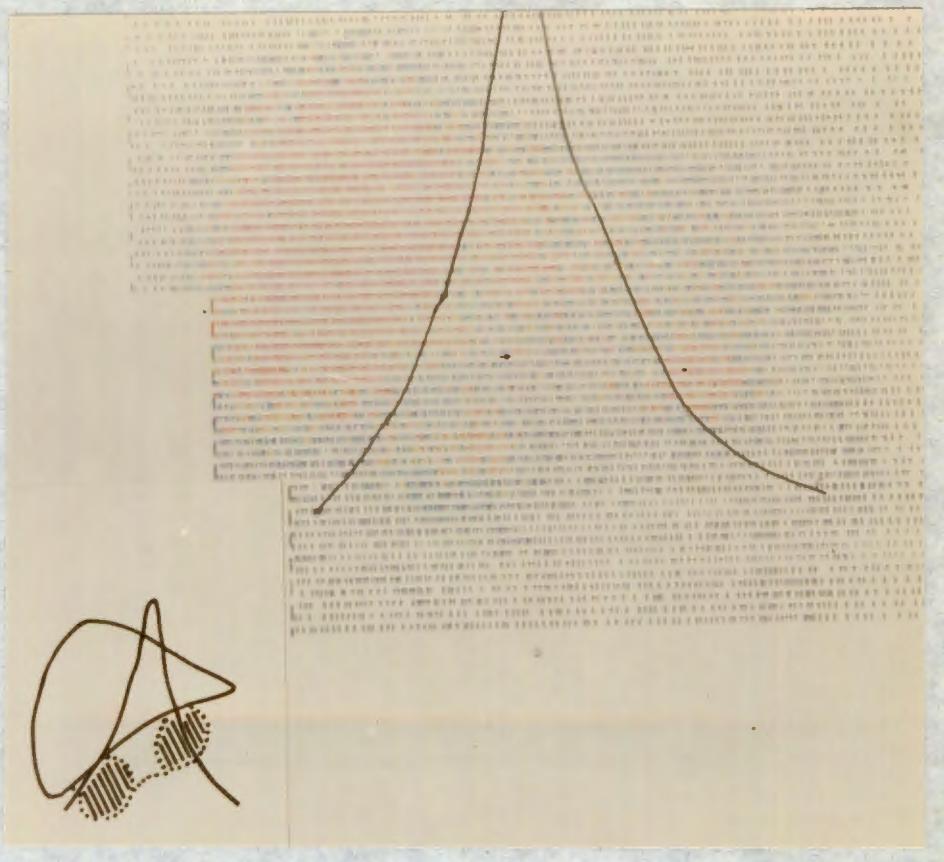

Fig.3.21:(Patient 17): This colour scan depicts a large filling defect in the midportion of the pancreas. It was due to a fusiform aneurysm of the aorta compressing the pancreas posteriorly.

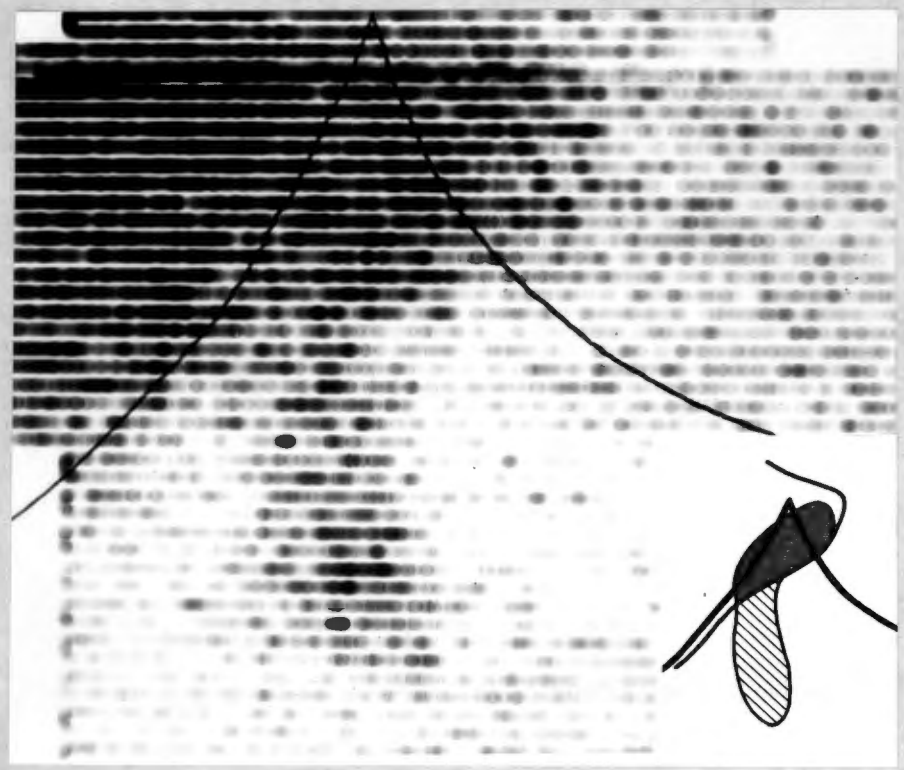

Fig.3.22:(Patient 18): Photoscan of a pancreas which is displaced upwards under the left lobe of the liver by a large saccular aneurysm of the abdominal aorta.

Another variation in the scan was upward displacement of the pancreas by an adjacent saccular aneurysm (Fig.3.22). Besides the very marked displacement the pancreas appeared otherwise normal.

iv) Postgastrectomy, Gastroenterostomy and Vagotomy

In this group 6 of 11 patients had normal scans. In 4 patients uptake was poor and this is particularly apparent in the head of the pancreas.

v) Diseases Associated with Cholestatic Jaundice

The pancreas scan was normal in the 5 patients with bile-duct carcinoma and in the 5 patients with intrahepatic cholestasis.

vi) Mesenteric Fibrosis

There was a circumscribed indentation of the neck and head of the pancreas in the patients with Gardner's Syndrome. This was due to a large fibrotic mesenteric mass indenting the pancreatic parenchyma.

vii) Sarcoidosis

There were 4 patients in this group. In 3 patients with parotid involvement and a positive Kveim test, uptake wasnormal in one and abnormally low in 2.

In 1 patient the scan was unreadable due to hepatomegaly .

viii) Miscellaneous

Normal pancreatic scans were obtained in all patients of this group.

Part 5. The Diagnostic Accuracy of Scanning

Forty consecutive scans were reported on without knowledge of any clinical detail. These patients were chosen and the scans were superivised by a colleague.

The cases in this study are tabulated in Table 3.6

Table 3.6

Diagnostic Assessment of the Pancreatic Scans of 40 Consecutive Unselected Patients

	Number in Group	Number correctly Diagnosed
Normal:	23	21
Abnormal:		
Carcinoma of the pancreas	2	1
Acute and chronic pancreatitis	8	8
Diabetes mellitus	4	4
Postgastrectomy, vagotomy, etc.	3	3
TOTAL	40	37

Scans were designated either normal or abnormal. Because the experience of the first 160 patients had indicated the variety of pathology which could influence pancreatic ^{75}Se - selenomethionine uptake, no attempt was made to state a definitive diagnosis. Instead a list of the diagnostic possibilities was stated in order of probability.

Result: (Table 3.6).

There were 3 errors in diagnosis. One patient whose scan was believed to be normal had a carcinoma in the area between the head and body of the

pancreas. This region had been passed over as normal physiological thinning on the initial reading but a review of the scan showed a circumscribed filling defect. This is clearly a fault of interpretation.

In 2 patients the scan was thought to show a generalized diminution of uptake. In neither of these patients was there biochemical or clinical evidence of pancreatic disease. Both patients were over the age of 65 years.

Part 6. Discussion

Since the introduction of ^{75}Se - selenomethionine there have been numerous reports describing various features of the normal and abnormal pancreatic scan. (Blau, 1964; Sodee, 1964; Beierwaltes, 1964; Haynie, Svoboda and Zuidema, 1964; Rodriguez - Antunez, 1964; Burke and Goldstein, 1964; Burdine and Haynie, 1965; Lahdevirta and Haikonen, 1965; Diethelm and Haacke, 1965; Sodee, 1965; Rodriguez - Antunez, Filson, Sullivan and Brown, 1966; Van Vaerenbergh, Van Vaerenbergh, Demeulenaere, Yvergneaux and Barbier, 1966; King, Sharpe, Grubb, Brock and Greenberg, 1966; ~~Mizukami, 1966;~~ Centi Colella and Pigorini, 1967; Brown, Sircus, Smith, Donaldson, Dymock, Falconer and Small, 1968). However, there has been no systematic attempt by any author/s to document fully the variations of normality and the patterns of abnormality.

A variation in the position and shape of the normal pancreas has been reported by Diethelm and Haacke (1965), Rodriguez - Antunez, Filson, Sullivan and Brown (1966), King, Sharpe, Grubb, Brock and Greenberg (1966), Centi Colella and Pigorini (1967) and Kaplan, Ben-Porath, Fink, Clayton and Jacobson (1966). The experience of this study has been similar, though a truly "horse - shoe" shaped pancreas (King, Sharpe, Grubb, Brock and Greenberg, 1966) has not been encountered amongst the normal scans. I believe that such a shape is very uncommon, and that a mistaken interpretation of a "horse-shoe" shape may be made when considerable bowel uptake of the isotope occurs (Fig.3.9). De Nardo, Crowley, Pardoe and Weintraub (1967) claim to have demonstrated in dogs that the total duodenal mucosal uptake of selenomethionine is about half of that in the pancreas. The observations in human scans supports this though there is great variation in bowel uptake from patient to patient. The constancy of the extrapancreatic shadow strongly suggests intramural uptake of the isotope in a relatively fixed position of the bowel wall rather than the passage of secreted enzymes along the bowel lumen. Its presence in some patients with absent or very poor pancreatic uptake

and the constancy of its position in different timed scans in the same individual, is additional evidence in favour of intramural uptake.

Attempts at the physical displacement of the liver edge by positioning the patient have not produced a convincing improvement in the quality of the scan and overlap persists (Diethelm and Haacke, 1965; Rodriguez-Antunez, Filson, Sullivan and Brown, 1966; Centi Colella and Pigorini, 1967). A lead shield placed over the liver after determining its position by an ^{198}Au colloidal gold scan (Sodee, 1964; Diethelm and Haacke, 1965) has also been unsuccessful in improving the quality of the scan. Burke and Goldstein (1964) tried unsuddessfully to block the hepatic uptake of selenomethionine by feeding their patients supplementary methionine in the diet for a few days prior to the pancreatic scan.

The most promising development in separating hepatic from pancreatic uptake comes from Kaplan, Ben-Porath, Fink, Clayton and Jacobson (1966) who used a dual - channel scanning machine. This technique permits either electronic subtraction of the liver from the print - out or simultaneous display of liver and pancreas in separate colours. A similar subtraction technique has also been described by Eaton, Potsaid, Lo and Beaulieu (1967). The presence of some overlap however does not necessarily invalidate the scan although it tends to limit its diagnostic value if the pancreas is abnormal. It should always be possible to discern an area of reinforcement in the hepatic shadow which conforms to the contour of the pancreas. Complete absence of this reinforcement in the experience of this study has invariably been associated with significant disease of the pancreas.

The best documented abnormality of the pancreatic scan is carcinoma (Blau, 1964; Sodee, 1964; Rodriguez-Antunez, 1964; Haynie, Svoboda and Zuidema, 1964; Burke and Goldstein, 1964; Burdine and Haynie, 1965; Lahdevirta and Haikonen, 1965; Van Vaerenburgh, Van Vaerenburgh,

Demeulenaere, Yvergneaux and Barbier, 1966; Rodriguez - Antunez, Filson, Sullivan and Brown, 1966; Kakehi, Tateno, Uchiyama and Tsuchiya, 1967; Kaplan, Ben-Porath, Fink, Clayton and Jacobson, 1966; Tebem, Keamey and Dolbow, 1965). Under ideal conditions it is possible for a 2 to 3 cm. diameter tumour to be detected. However, as stressed by Laconi, Melfi, Cataliotti and Semilia (1965) this probably depends in part on the position of the growth in the pancreas. Small localised lesions towards the edge of the gland being better detected than if situated in the middle of the parenchyma, of the head for example.

Rodriguez-Antunez (1964) and Kakehi, Tateno, Uchiyama and Tsuchiya (1967) have suggested the following signs as indicative of a pancreatic tumour on the scan:-

a) a localized filling defect;
b) displacement of pancreatic tissue outside the normal outline of the pancreas;
c) distortion and narrowing of any segment of the organ;
d) lack of visualization of all or part of the gland;
e) a filling defect in the liver scan.

However it is apparent from this study that all these features can be caused by a variety of pancreatic or extrapancreatic pathology other than neoplasia. Of the features listed, the abnormality most suggestive of an intrinsic neoplasm is a localised filling defect within the substance of the pancreas parenchyma especially if it has a concave rounded edge (Fig.3.11). Attention to this particular detail should have avoided the error of interpretation made in the blind study reported on page.111 . Involvement of the pancreas by secondary carcinoma may result in displacement of the tissue outside the normal contour though this is admittedly a very uncommon occurrence. However, the presence of a pseudopancreatic cyst may show as an area of more extensive activity related to the body and tail of the pancreas (Fig.3.17). Distortion and

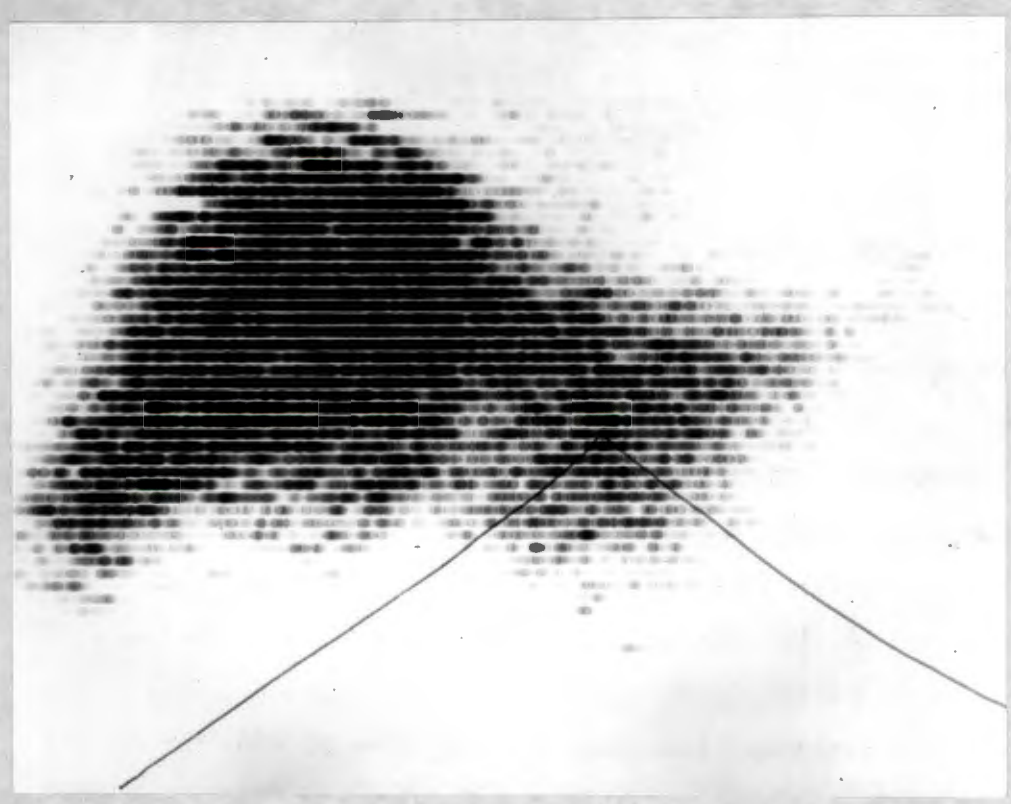

Fig.3.23:(Patient 5): Photoscan of a ^{198}Au colloid gold liver scan showing a pseudofilling defect between right and left lobes of the liver. This patient had a carcinoma of the head of the pancreas with common bile-duct obstruction. There were no metastases detected in this position at laparotomy.
Page 118.

narrowing of any segment of the organ may occur with any mass adjacent to the pancreas (Fig.3.21). Lack of visualisation of the entire or part of the gland may occur with a variety of conditions such as acute or chronic pancreatitis, cholelithiasis, diabetes mellitus and postgastrectomy, gastroenterostomy or vagotomy: This is certainly the least specific of the "carcinoma signs" and should be interpreted with caution. In complete common bile-duct obstruction it is common to find a filling defect on the hepatic scan between the right and left lobes of the liver (Fig.3.23). This occurs irrespective of the cause of the obstruction and is believed to be a consequence of the obstruction itself. The defect does not necessarily represent tumour invasion of the liver substance. It was present to a greater or lesser degree in all the patients with carcinoma of the common bile-duct whether or not the carcinoma was actually involving the liver substance. On the basis of this study it would seem as if the two changes most suggestive of carcinoma are -

i) a localised circular filling defect (Fig.3.11) or

ii) distortion and disruption of the normal pancreatic contour, possibly associated with a filling defect as well, such as is illustrated in Fig.3.13).

However, that even these signs cannot be interpreted dogmatically is clear from the experience of the scan depicted in Fig.3.24). This patient was submitted to an elective re-exploration of the pancreas on the basis of this scan as it seemed almost certain that he was harbouring a carcinoma. This impression was strengthened by the history or relapsing pancreatitis. The changes were due however to a pancreatic infarct without a trace of neoplastic tissue on microscopic examination of the resected specimen.

The problem of enhanced uptake by normal or neoplastic tissue is much more difficult to assess. In the case of the poorly differentiated α - cell islet tumour presented (Fig.3.14a), the gland was the seat of chronic pancreatitis severe enough to limit almost completely the uptake in head and neck.

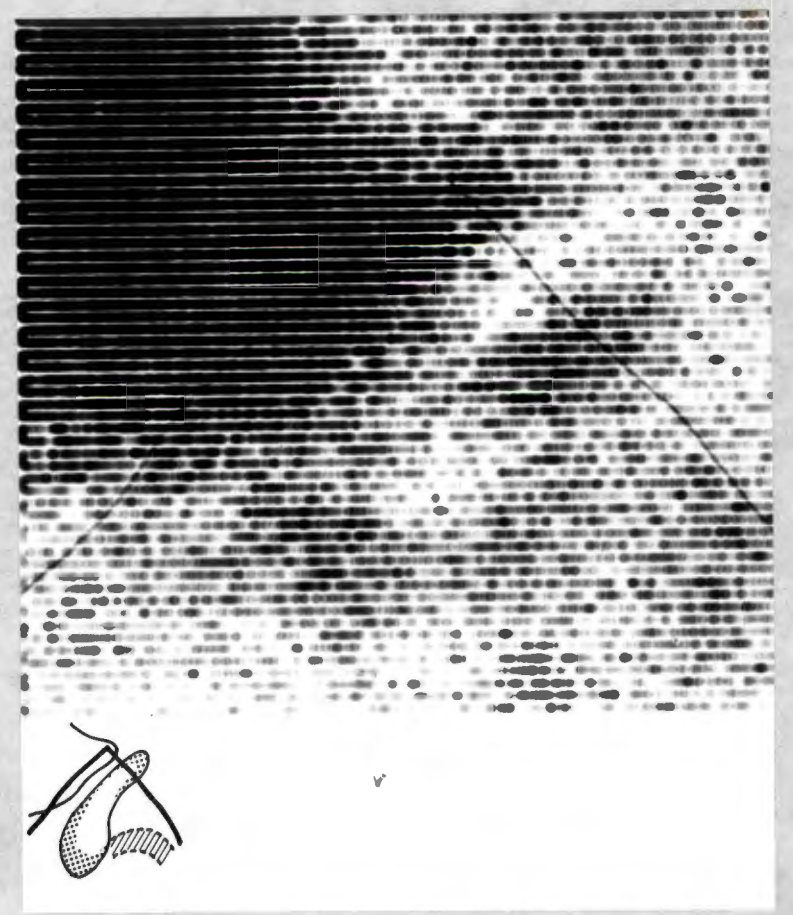

Fig.3.24: (Patient 11): Photoscan depicting a filling defect in the body and tail of the pancreas. This was due to an infarcted necrotic area of pancreatic parenchyma associated with relapsing pancreatitis. Page 118 .

The very considerable isotope concentration in the tail in an area largely occupied by the infiltrating functioning carcinoma suggested a situation analogous to selenomethionine. concentration by functioning parathyroid adenomas (Potchen, Wilson and Dealy , 1965). A follow-up scan in this patient 4 months after a distal pancreatectomy showed disappearance of the active area (Fig.3.14b). At this time the basal acid output had decreased from 20mEq/hour pre-operatively to 5 mEq/hour after the operation. Burke, Finer and Sandlow (1964) have reported a localized functioning non - β islet cell tumour nodule associated with the Zollinger- Ellison Syndrome and hypercalcaemia in which the pancreatic scan showed a filling defect in the body of the pancreas. On the other hand the patient reported in this study had a diffuse lesion with no recognisable tumour nodules. Brown, Sircus, Smith, Donaldson, Dymock, Falconer and Small (1968) report the case of a pancreatic tumour associated with gastric hypersecretion and potassium - losing watery diarrhoea in which the pancreatic scan showed "an enormously increased uptake throughout the whole pancreatic mass". There may be local metabolic and vascular factors responsible for the difference in scanning appearance. For example, in advance lymphosarcoma there may be a high uptake of ^{75}Se - selenomethionine but not in the early lesion (Herrera, Gonzalez, Schwartz, Diggs and Belsky, 1965). The question of selenomethionine concentration by functioning tumour tissue must await further experience with these rare tumours. Analyses by Gregory and Tracy (1966) of human gastrin, have shown that it contains methionine. Because there is no methionine in insulin, an insulinoma would be expected to manifest as a filling defect on the scan. This supposition is supported by the case presented by Haynie, Svoboda and Zuidema (1964) and that reported by Brown, Sircus, Smith, Donaldson, Dymock, Falconer and Small (1968).

It would appear that any condition preventing the normal synthesis of digestive enzymes by the pancreas is likely to manifest as diminished or absent uptake of ^{75}Se - selenomethionine on the scan. Acute or chronic pancreatitis

may produce such a picture. In chronic pancreatitis with clinical evidence of exocrine insufficiency, diminished or absent uptake is the rule (Fig.3.16a). This is also the experience of Sodee (1964), Burdine and Haynie (1965), Lahdevirta and Haikonen (1965) and Centi Colella and Pigorini (1967). In acute pancreatitis uptake is impaired in part (usually the head and neck) or whole of the pancreas. However here clinical recovery may be associated with restoration of the pancreatic scan to normality (Fig.3.16b). In all of the patients in this study scanned more than 3 weeks after the attack, the pancreas appeared normal. This observation is paralleled by the results of function tests. Lagerlof (1939) and Dreiling and Janowitz (1962) observed a diminution of enzyme secretion for a variable period after an attack of acute pancreatitis. The volume and bicarbonate output recovers much more rapidly than enzyme output and may be normal 4 days after an acute attack (Dreiling and Janowitz, 1962). These findings, together with the scan observations suggest that recovery of full acinar function after an attack of acute pancreatitis is slower than the recovery of duct function.

The great majority of scans performed on patients with pseudocysts of the pancreas have been reported as showing areas of diminished uptake (Beierwaltes, 1964; Haynie, Svoboda and Zuidema, 1964; Tabern, Kearney and Dolbow, 1965; Van Veerenburgh, Van Veerenburgh, Demeulenaere, Yvergneaux and Barbier, 1966; Centi Colella and Pigorini, 1967). It is not possible to ascertain from the literature how many of these reports have been confirmed at laparotomy. By contrast in the cases of this study the pancreatic pseudocyst is seen as an area of increased activity overlying the body and tail of the pancreas (Fig.3.17). This apparent discrepancy almost certainly depends on whether or not the pseudocyst communicates with the pancreatic duct system. If the pseudocyst represents a "sympathetic" effusion in the lesser sac then compression of the pancreas anteriorly by the pseudocyst would produce a filling defect on the scan. However communication of the pancreatic duct system

with the cavity of the lesser sac will result in the leakage of ^{75}Se - seleno-methionine labelled enzymes into the pseudocyst with the appearances on the scan described above. The case report by Kaiser, Roth and Bockus (1955) demonstrates that at least in some patients with pseudocyst, the enzyme (amylase, lipase) content of the pseudocyst fluid may parallel that found in the pancreatic duct.

The pancreatic uptake of isotope is frequently diminished in patients with diabetes mellitus. This observation agrees with the experience of Sodee (1965) and of Lahdevirta (1967). The latter author related the secretin response to the quality of the scan in 27 hospitalized diabetic patients. Although he was measuring duct (that is, response to secretin) rather than acinar function he found that in 8 of 12 insulin dependant diabetics there was no pancreatic uptake on the scan. He stated that in general "the lowered pancreatic uptake corresponds fairly well to the pathological result in the secretin test". There have been several studies reporting decreased volume and bicarbonate and enzyme secretion by the pancreas in patients with diabetes mellitus (Jones, Castle and Mulholland, 1925; Lagerlof, 1939; Pollard and Miller, Brewer 1943; Vacca, Henke and Knight, 1964; Chey, Say and Shuman, 1963; Bock, Bank, Marks and Jackson, 1967). Although this observation does not appear to be of much clinical significance it is important to realise that marginally decreased pancreatic function and a poor scan in a diabetic subject does not necessarily imply underlying pancreatitis or carcinoma but may be an association of the diabetic condition per se.

The finding of 4 cases of "silent" pancreatitis in the group of patients with cholelithiasis parallels the experience of Sodee (1965) and Brown, Sircus, Smith, Donaldson, Dymock, Falconer and Small (1968) who also noticed that some patients with cholelithiasis concentrate the isotope poorly in the pancreas. This observation is presumeably associated with the presence of some structural

change in the parenchyma because 3 of the 4 patients in this study, at operation were found to have induration of the pancreas. The relationship between these conditions however remains obscure.

The reduced isotope uptake in at least 4 of the 11 patients who have undergone gastric surgery may indicate the importance of an intact upper gastro-intestinal tract for optimum pancreatic function. Gastroenterostomy or Polya gastrectomy will bypass the duodenal loop and exclude the most important physiological mediators of pancreatic enzyme release. Partial gastrectomy which almost invariably sacrifices the gastric antrum may be associated with the loss of the pancreatic enzyme and volume response to gastric distention (White, Hayama and Magee, 1960; Harper, Blair and Scratcherd, 1963). The vagus has been demonstrated to have a permissive action on pancreatic enzyme and fluid secretion (Brown, Harper and Scratcherd, 1967). Vagotomy will tend to minimize the pancreatic response to humoral mediators of secretion (Pfeffer, Stephenson and Hinton, 1952).

The failure of isotope uptake in the one patient with fibrocystic disease was adequately accounted for at autopsy with the demonstration of extensive fibro - fatty replacement of the pancreatic parenchyma. This very limited experience paralleled that of Quinlan, Way and Joske (1967) who record the case of a 28 year old man with small bowel obstruction due to "meconium ileus equivalent". The patient had no uptake of ^{75}Se - selenomethionine on pancreatic scanning. The parencymal atrophy and fibro - fatty replacement in the case reported in this study is said by Bodian (1952) to occur characteristically in older children suffering from this disease.

Absence of uptake in the patient with extensive primary amyloidosis was associated with extensive pancreatic parenchymal involvement by amyloid at autopsy. In spite of the absence of a family history the extensive neuro-

logical and gastrointestinal involvement by amyloid in this patient was very similar in distribution to that occurring in the syndrome of familial amyloidosis described by Andrade (1952).

The poor pancreatic uptake in 2 out of 3 patients with a positive Kveim test and paroid enlargement cannot be accounted for on the data available. As yet none of these patients have had formal pancreatic function tests. Clinical symptoms due to pancreatic disease in patients with sarcoidosis would appear to be a rare occurrence and case reports of this association are few (Ekelund, 1946; Curran and Curran, 1950).

There have been few attempts to correlate the results of the conventional pancreatic function test with the changes seen on scanning. The study by Lahdevirta (1967) relating the pancreatic secretin response to the uptake of ^{75}Se - selenomethionine as seen on scanning in diabetic patients suggested a general concordance of results. Brown, Circus, Smith, Donaldson, Dymock, Falconer and Small (1968) studied 20 patients by both pancreatic scanning and by the pancreatic function test of Marks and Tompsett (1958) utilizing secretin and pancreozymin injections. Twelve scans were normal, and in these patients conventional tests were normal in 9 and abnormal in 3. It seems probable from the clinical details that in at least 2 of the 3 patients the pancreas was structurally normal. Eight scans were abnormal and in 7 of these patients the conventional tests were also abnormal. These authors concluded that there was "a notable degree of agreement between the two techniques".

In assessing the diagnostic accuracy of scan reporting, three mistakes were made in 40 consecutive patients scanned. The scan was viewed without having seen the patient and without any knowledge of the clinical details. This represents an accuracy of over 90% in answer to the question "Is this patient's pancreas normal or abnormal ?" As there is no other report in the literature of an assessment of scan reporting under conditions as stringent as this it is impossible to compare

this series with any other. In this writer's experience bias resulting from previous examination of the patient or the knowledge of clinical detail, or an earlier viewing of the scan may influence any subsequent assessment. It is felt that in general the most useful assessment of the pancreatic scan would come from first viewing the scan without any knowledge of the patient and then with full details of the patient's clinical status. This should permit more accurate assessment of borderline cases and permit a re-assessment in patients in whom signs may have been misinterpreted. The overall impression has been gained from this study that in patients in whom the pancreatic ^{75}Se - selenomethionine uptake has been designated as "very good" or "excellent" throughout the organ, the likelihood of occult underlying pancreatic disease is very remote. This is similar to the experience of Sodee (1965)[7].

Part 7. Conclusions

In general a wide variety of disease processes involving the exocrine pancreas are likely to diminish uptake of ^{75}Se - selenomethionine by the pancreas. From the experience of this study the majority of abdominal scans do not offer a definitive pathological diagnosis on the features of the scan alone. In these cases ultimate interpretation of the scan, as with most ancillary investigations must be related to the clinical picture and the results of other investigations.

The two most distinctive abnormalities seen on scanning were those due to pseudopancreatic cyst (Fig. 3.17) and extrinsic displacements of the pancreas (Fig.3.19 , 3.22). It should be possible on the basis of these distinctive patterns to make a diagnosis from the appearance of the scan alone i.e. whether the abnormality is due to a pseudopancreatic cyst or extrinsic displacement of the pancreas. The signs most suggestive of carcinoma of the pancreas are a localised filling defect within the substance of the gland or a filling defect with disruption of the normal pancreatic morphology (Fig.3.13). In a patient with acute pancreatitis and generalised failure of ^{75}Se - selenomethionine uptake by the pancreas, the presence of an underlying pancreatic carcinoma cannot be excluded by scanning.

In general, the finding of an unequivocally normal scan can be taken as strong evidence against there being significant pancreatic disease present.

CHAPTER 4

AN EVALUATION OF ^{75}Se - L - SELENOCYSTINE AND ^{75}Se DLmeso - SELENOCYSTINE AS PANCREATIC SCANNING AGENTS.

There is no information concerning the suitability of ^{75}Se - selenocystine as a scanning agent and a paucity of information about its metabolism.

Considering the similarities in the metabolism of methionine and selenomethionine, it was felt on theoretical grounds at least that the metabolism of selenocystine would parallel that of cystine.

In a study comparing the fate of injected ^{75}Se-selenomethionine and ^{75}Se-selenocystine in rats, Anghileri and Marques (1965) reported that the selenoamino acids showed a similar pattern of incorporation with comparable pancreatic specific activity at 8 hours. This finding is in keeping with Blau's (1964) observation in dogs in which he found comparable pancreatic incorporation of ^{14}C -L - methionine and ^{35}S - L - cystine at one hour (Table 3. 1.). Therefore it was felt that ^{75}Se - selenocystine could possibly represent an alternative agent to ^{75}Se - selenomethionine for pancreatic scanning.

This study was undertaken primarily to assess the value of ^{75}Se - selenocystine as a pancreatic scanning agent. Both the DLmeso-and L - configurations of ^{75}Se selenocystine are compared with ^{75}Se - L - selenomethionine in the rabbit and in man. Initially, DLmeso-selenocystine was the only form of the radioactive compound available. This meant that the molecule was partly in the unnatural D- configuration and as a result the tissue uptake and metabolism would probably differ from the natural L - selenocystine. A number of experiments were repeated for comparison when ^{75}Se - L - selenocystine became available.

Part 1. Potential Hazards in the Use of ^{75}Se - Selenocystine

Radiation Dosimetry

For the purpose of the dosimetry calculation it was assumed that the biological behaviour of selenocystine would parallel that of cystine. This was shown to be correct in animal studies in that approximately 50% of the injected activity was excreted within the first 24 hours (Table 4.12.). In additon it was demonstrated that with the exception of the pancreatic activity, the distribution of activity in two rabbits seven days after an intravenous injection of ^{75}Se - L - selenomethionine and ^{75}Se - L - selenocystine (30μCi /Kgm. body weight of each) respectively, was comparable. However, because of the initially high excretion, whole body radiation from this compound would almost certainly be less.

The radiation dosage calculated on the basis of 4μCi/Kgm. for selenocystine is comparable to that of selenomethionine at 3μCi/Kgm., thus introducing a safety factor. This is contained in Appendix 2. On the basis of these calculations permission was granted for the use of ^{75}Se - selenocystine in humans at a dose of 3μCi/Kgm. body weight.

Toxicity of Selenocystine

Klug, Moxon, Petersen and Painter (1953) calculated that the LD50 of D, L., DL or meso-selenocystine in rats injected intraperitoneally was 4.0 (±0.2) mgs. Se/Kgm. body weight. ~~Extrapolated~~ Related to man (70 Kgm.) this would represent 2,500 to 3,000 times the quantity of selenocystine administered in these studies.

Cystine if administered parenterally may present problems through crystallization in the urinary tract. This however is a dose related phenomenon and is unlikely to be a problem with the quantities used in these studies. For example, the available ^{75}Se - selenocystine (Amersham) has a specific activity of 177 mCi/mM. A 3 to 4 μCi/Kgm dose to an adult would contain 180 to 240 μGms. of selenocystine. The normal excretion of cystine is 40 to 80 mg. per day (Harris, Mittwoch, Robson and Warren, 1955).

In order to ensure stability selenocystine compounds have to be dissolved in 0.1N hydrochloric acid. This injection, though administered rapidly proved painful to the patient and was usually associated with phlebitis at the site of injection.

Part 2. Material and Methods

^{75}Se - Selenocystine Compounds

The compounds used were:-

i) ^{75}Se DLmeso - selenocystine. This was supplied as 1.09 mCi dissolved in 170 mgs. 0.1N hydrochloric acid. The specific activity was 177 m Ci/mM and the selenocystine content 2 mgs.

In the human studies the volume was made up to give a final concentration of 1 mCi/ml. in 0.1N hydrochloric acid. This concentration permitted small volume injections using a finely graduated one millilitre syringe.

In the animal studies a separate batch of the same isotope was used with the same initial concentration and specific activity. This was done both for hygienic reasons and to check the consistency of behaviour of different batches of the isotope. The initial volume was diluted to ten millilitres permitting more accurate estimation of the lower dose requirements of the rabbits.

ii) ^{75}Se - L - selenocystine. This compound was supplied as 2 mgs. of selenocystine dissolved in 2.14 mgs. of 1N hydrochloric acid and having 2.0 m Ci total activity. The specific activity was 332 m Ci/mM. This was diluted tenfold first with sterile distilled water to give a final acid concentration of 0.1N. The solution was made up to 2 ml. with 0.1N hydrochloric acid, and then divided into two one millilitre (1 m Ci) portions in separate sterile dark-glass containers. In the human studies the compound was used in this concentration (1 m Ci/ml.). For the rabbit studies it was further diluted to a concentration of 100 μ Ci/ml. with 0.1N hydrochloric acid.

Both compounds were synthesized and supplied by the Radiochemical Centre, Amersham, Buckinghamshire, England, both sulphur atoms of the individual cystine molecule are replaced by ^{75}Selenium in ^{75}Se - selenocystine. *

* Personal communication: Dr.J.Ogle. Head of the Inorganic Chemistry Department, The Radiochemical Centre, Amersham.

A. Animal Experiments.

i) Whole Body Counting of Rabbits

Whole body retention of intravenously injected ^{75}Se - seleno-methionine, ^{75}Se - DLmeso and ^{75}Se -L - selenocystine was followed in six young ($1\frac{1}{2}$ to $2\frac{1}{2}$ Kgm.) New Zealand and Dutch rabbits (two rabbits for each compound) over one week: Each rabbit received 50 to 60 μCi of the ^{75}Se - selenoamino acid via an ear vein. The whole body count immediately after the isotope injection was taken as 100% retention.

The rabbits were placed in a perspex box of internal dimensions 34 cm. long X 14 cm. wide X 20 cm. deep with ventilation grills at either end. The box was placed with its centre 50 cm. from the face of the whole-body scintillation counter. This consisted of a 12.5 cm. diameter X 10 cm. thick thallium-activated sodium iodide (Na I (Tl)) crystal mounted in a 5 cm. thick shield of aged lead. A single-channel pulse height analyser was used to select counts in an energy band 100 to 400 KeV (corresponding to the 270 and 280 KeV gamma emission energies of ^{75}Se).

Two counts of 100 second duration were taken, the perspex box being rotated through 180° between the two so that the rabbit was counted from both right and left-hand sides. A small bottle containing approximately 10 μCi ^{75}Se was counted as a standard each time so that correction could be made for radioactive decay and for any variations in the efficiency of the counter.

The daily counts were corrected for background and radioactive decay was expressed as a percentage of an initial value taken 1 to 2 hours after the injection of the radioactive dose.

ii) Scanning of Rabbits

The six rabbits used for whole-body counting were scanned 30 minutes and 5 hours after the isotope injection.

The scans were performed with the Picker Magna - Scanner V (Picker X-Ray Corporation, New York) on similar settings used for the ^{75}Se - selenomethionine human scans (Chapter 3).

A "fine-focus" collimator of nominal focal length 7.5 cm. was used and a scanning speed of 24 cm./min. The rabbit was anaesthetised by an intravenous injection with Nembutal (pentobarbital) (28 mgs./Kgm. body weight) followed by open-mask ether anaesthesia. Where necessary and was held in position by straps passed round all four legs and fastened to the scanning couch and by a band of thin gauze across the abdomen.

iii)a. Organ Distribution of Injected Isotope

In this study the tissue distribution of ^{75}Se - selenomethionine was compared to that of ^{75}Se - L - selenocystine. Three young Dutch rabbits (1½ to 2 Kgm.) were used. One was injected with ^{75}Se - selenomethionine and two with ^{75}Se - L - selenocystine (30μCi/Kgm.).

Following the injection of selenoamino acid the rabbits were anaesthetised with Neanbutal (28 mgs./Kgm.) and heparinised by the intravenous injection of 3000 u of heparin sulphate. After immobilisation of the rabbit on a dissecting table, the external carotid artery was cannulated with a polythene catheter which passed into a flask strapped below the head of the rabbit. The catheter was filled with saline and the lumen occluded by an artery clip.

Twenty minutes after the isotope injection the clip was released and the animal gradually exsanguinated under anaesthesia. The average time for exsanguination was always about 35 to 45 minutes. The time taken from injection of the isotope to death of the rabbit averaged 60 ± 10 minutes in all animals.

The liver, pancreas, stomach, small bowel, kidneys, spleen, gonads and heart were then removed washed under a tap and dried with gauze swabs. The bowel was opened longitudinally and the mucosal surface washed free of food particles and debris. The organs were weighed and secured in disposable plastic Petri dishes.

iii)b. Counting of Rabbit Organs

Counting was performed with the same scintillating crystal as was used for whole-body counting, but pointed vertically downwards. The distance from the crystal surface to the base of the Petri dish placed below it was 10 cm. except in the case of the liver when a 50 cm. distance was used because of the much greater radioactivity in this organ.

Two standards, equal to 1% and 10% respectively of the dose given to the rabbit, were prepared (by volume) in small sealed bottles which were placed inside Petri dishes and counted under the same geometrical conditions as the rabbit organs; the letter standard was used only for comparison with the liver samples. All samples were counted for times long enough to ensure that the error due to counting statistics was not greater than 1%.

B. Human Studies

i) Human Scans

The human scans were performed under similar conditions and with similar machine settings to those described for ^{75}Se - selenomethionine (Chapter 3). Scans were performed 1 hour and 5 hours after the injection of ^{75}Se - DLmeso - selenocystine and at 1 hour and 5 days after ^{75}Se - L - selenocystine.

Two patients were injected with ^{75}Se - DLmeso - selenocystine and one with ^{75}Se - L - selenocystine (3μ Ci/Kgm.). All three patients were volunteers to whom the purpose and potential hazards of the procedure had been fully discussed. In none of the three was there any clinical indication of pancreatic disease.

ii) Whole-Body Counting

Whole body retention of ^{75}Se - L - selenocystine was studied in the one patient. Readings were made daily for 5 days and then every second or third day for 28 days. The patient sat in a chair facing the scintillation counter at a 100 cm. from the crystal surface. The crystal was directed just below the level of the xyphisternum. Details of the whole-body scintillation counter specifications and settings are identical to those used for whole-body counting of the rabbits.

Part 3. Results

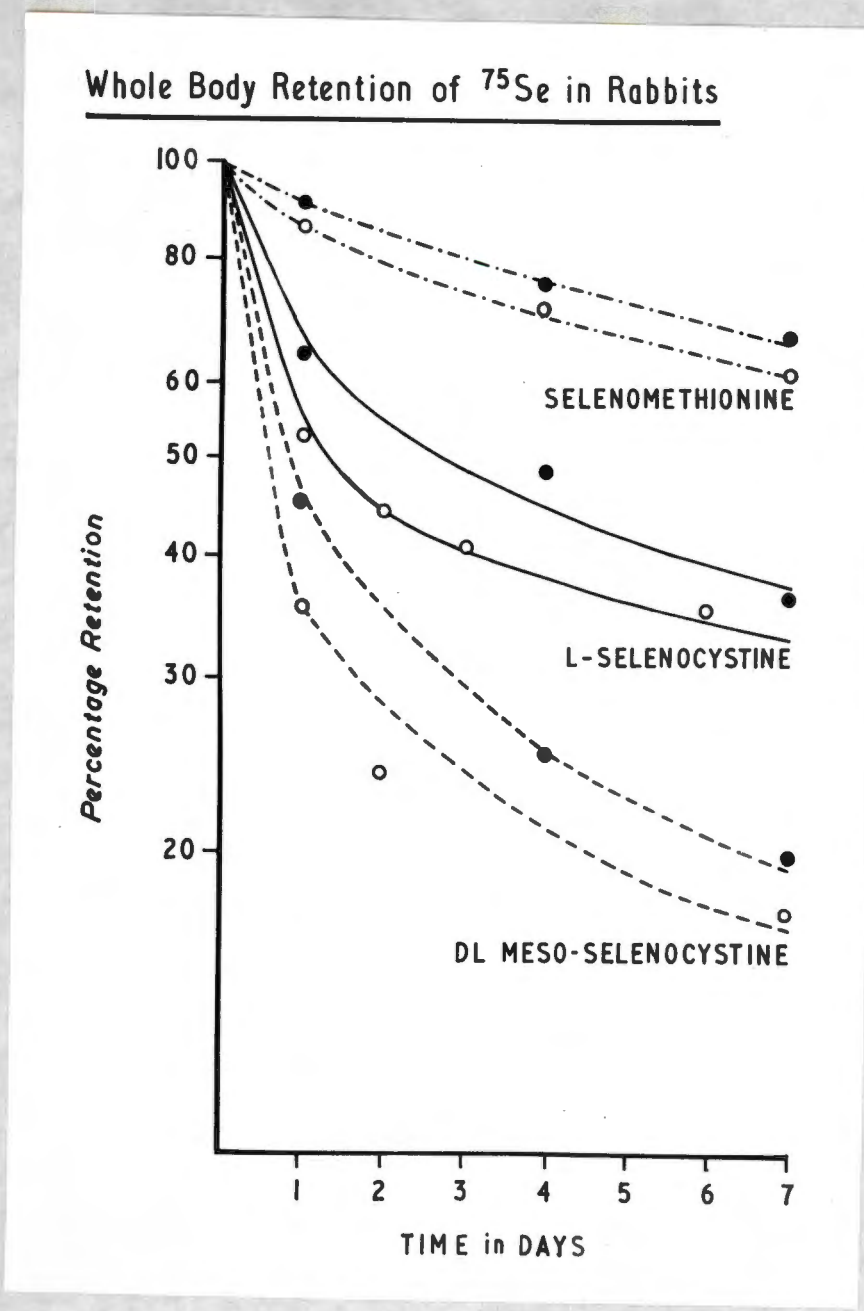
Whole Body Retention of ^{75}Se in Rabbits
100
80
60
50
40
30
20
Percentage Retention
SELENOMETHIONINE
L-SELENOCYSTINE
DL MESO-SELENOCYSTINE
1
2
3
4
5
6
7
TIME in DAYS

Fig.4.1:

a) Animal Experiments

i) Whole-Body Isotope Retention

The whole-body retention of the ^{75}Se - selenoamino acids over 7 days is plotted in Fig. 4.1.

Both forms of selenocystine are rapidly excreted. Table 4.1 depicts the isotope retention at 24 hours.

Table 4.1

Rabbit No.	^{75}Se - Selenoamino Acid	Retention at 24 hours (%)
1	^{75}Se - L - Selenomethionine	92
2	" " "	86 (mean = 89)
3	^{75}Se - DLmeso -Selenocystine	45
4	" " "	35 (mean = 40)
5	^{75}Se - L - Selenocystine	64
6	" " "	53 (mean = 59)

Retention of L - selenocystine is greater than that of the DLmeso - form but both forms of selenocystine are excreted in much greater quantity than selenomethionine in the first 24 hours.

ii) Abdominal Scans

The scans of only one rabbit of each pair will be presented as the features to be described were reproduced on each occasion for each agent used.

Fig.4.2(a):

^{75}Se – Dimeso-Selenocystine
Thirty minute scan.

Fig.4.2(b):

^{75}Se – L – selenomethionine
Thirty minute scan.

^{75}Se - L - Selenomethienine (Rabbits No's. 1 and 2)

a) Thirty Minute Scan (Fig 4.2a).

The early distribution of isotope showed major areas of activity in the liver, kidneys and bladder. A prominent area of activity medial to the right kidney was interpreted as being pancreatic uptake, possibly reinforced by adjacent, small-bowel and stomach. The right kidney impression has been reinforced by the right lobe of the liver accounting for the apparent density difference between right and left kidneys.

b) Five Hour Scan (Fig 4.3a).

Uptake in all viscera appears to have increased. This is particularly notable in the kidneys and bladder, the latter organ also being larger in size.

^{75}Se - DLmeso - Selenocystine (Rabbits No's. 3 and 4).

a) Thirty Minute Scan (Fig.4.2a).

The early distribution of isotope shows a striking concentration of activity in the liver, kidneys and bladder. The prominence of renal and bladder activity is accentuated by the lack of background activity in the rest of the abdomen.

b) Five Hour Scan (Fig.4.3a).

This scan shows a considerable reduction of renal activity with an increase in bladder activity. The bladder has increased in size.

Fig.4.3(a):

^{75}Se - DL - meso - selenocystine
Five hour scan.

Fig.4.3(b):

^{75}Se - L - selenomethionine
Five hour scan.

Fig.4.4(a):

^{75}Se - L - selenocystine
Thirty minute scan

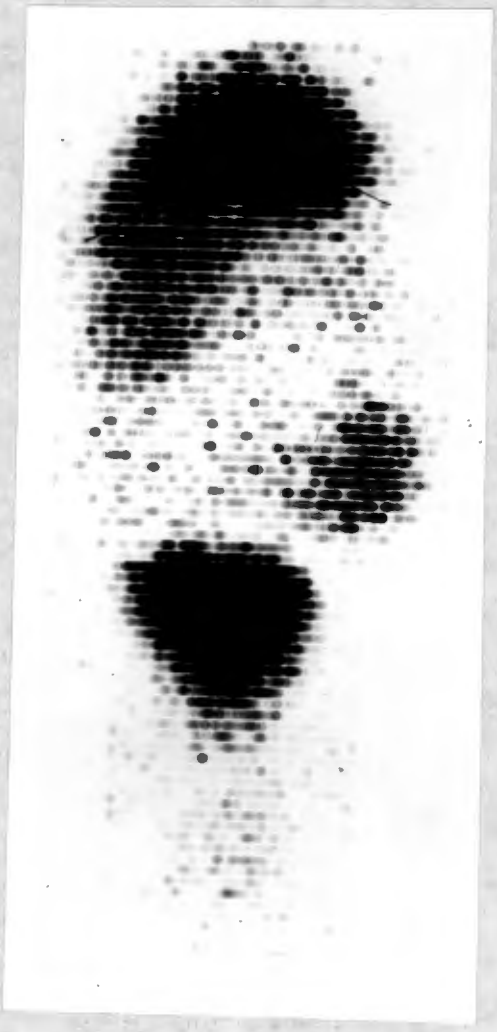

Fig.4.4(b):

^{75}Se - L - selenocystine
Five hour scan

(The gonads are included in both scans).

^{75}Se - L - Selenocystine (Rabbits No's. 5 and 6).

a) Thirty Minute Scan (Fig.4.4a).

This scan shows prominent uptake in the liver, kidneys, bladder, bowel and pancreas. The liver and renal uptake is particularly prominent.

b) Five Hour Scan (Fig.4.4b).

There has been an enormous increase in the activity and size of the bladder. Though the liver activity has increased the general background (small bowel and pancreas) activity has decreased.

iii) Organ Distribution of Injected Isotope

The organ distribution of injected isotope at one hour is given in Table 4.2 .

The pancreatic specific activity is greater than the hepatic in the case of ^{75}Se - selenomethionine. The reverse is true for ^{75}Se - selenocystine and the total hepatic activity for ^{75}Se - selenocystine is approximately twice as great as that of ^{75}Se - selenomethionine. Uptake in the stomach and small bowel is greater for ^{75}Se - selenomethionine than it is for ^{75}Se - selenocystine.

Renal activity is approximately twice as great for ^{75}Se - selenocystine than ^{75}Se - selenomethionine.

Table 4.2

Tissue Levels of the ^{75}Se - L - Selenoamino Acids One Hour After Intravenous Administration

Organ	^{75}Se - Selenomethionine		^{75}Se - Selenocystine			
	% Dose Gm. Tissue	% Total Dose in Organ	% Dose Gm. Tissue	% Total Dose in Organ	% Dose Gm. Tissue	% Total Dose in Organ
Pancreas	0.51	2.04	0.19	0.83	0.14	0.69
Liver	0.17	12.26	0.34	20.10	0.27	25.17
Small Bowel	0.20	6.31	0.06	2.20	0.04	1.27
Stomach	0.21	3.53	0.11	1.74	0.09	1.75
Kidneys	0.31	3.34	0.78	7.42	0.58	8.42
Spleen	0.16	0.14	0.10	0.05	0.06	0.04
Gonads	0.09	0.07	0.05	0.02	0.06	0.05
Heart	0.09	0.35	0.06	0.22	0.04	0.18

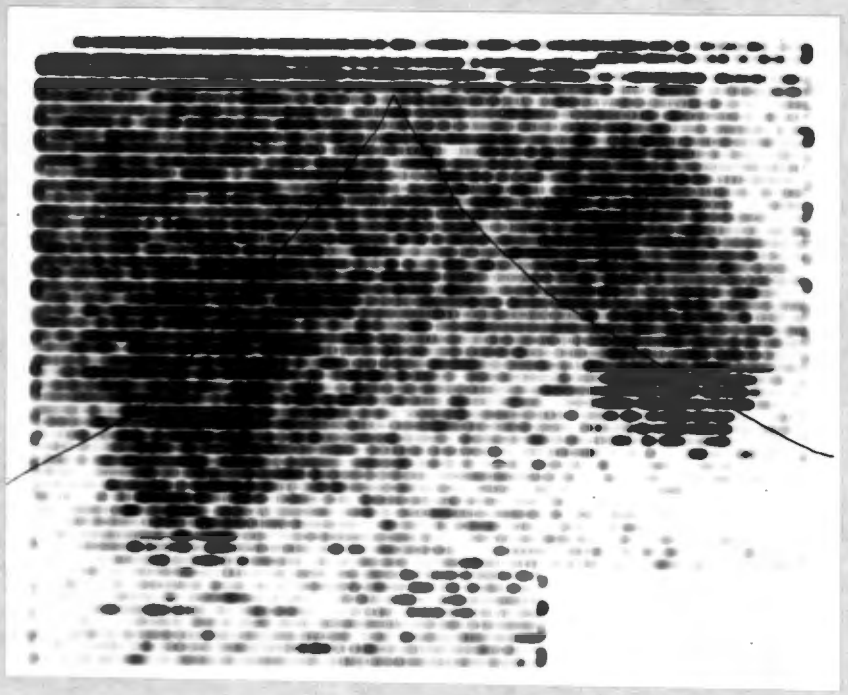

Fig.4.5: ^{75}Se - DLmeso - Selenocystine.
Human abdominal scan commenced 40 minutes after injection of the isotope. The black line represents the surface markings of the costal margin.

b) Human Studies

The ^{75}Se - DLmeso and L - Selenocystine Pancreatic Scan

The features of the pancreatic scans were similar for both compounds and they will be described together.

Patient No.1. ^{75}Se - DLmeso - Selenocystine

Fig. 4.5 shows the scan performed 40 minutes after the isotope injection. There is a marked renogram effect which was confirmed by the posterior scan (Fig.4.6) performed immediately afterwards. The position of the kidneys is well demonstrated.

In Fig. 4.7 a scan performed 5 hours after the injection of isotope shows a reduction in the renal density and of the reinforced density passing from the upper pole of the left kidney to the mid-portion of the right kidney. This was taken to represent pancreatic uptake.

Patient No. 2. ^{75}Se - L - Selenocystine

Fig. 4.8 also shows a prominent renogram effect. However pancreatic uptake is more easily discernable in this scan as a density passing obliquely down from the upper pole of the left kidney towards the mid-portion of the right kidney.

A scan performed 5 days later (Fig.4.9) shows a generalised reduction in organ activity with absence of pancreatic activity.

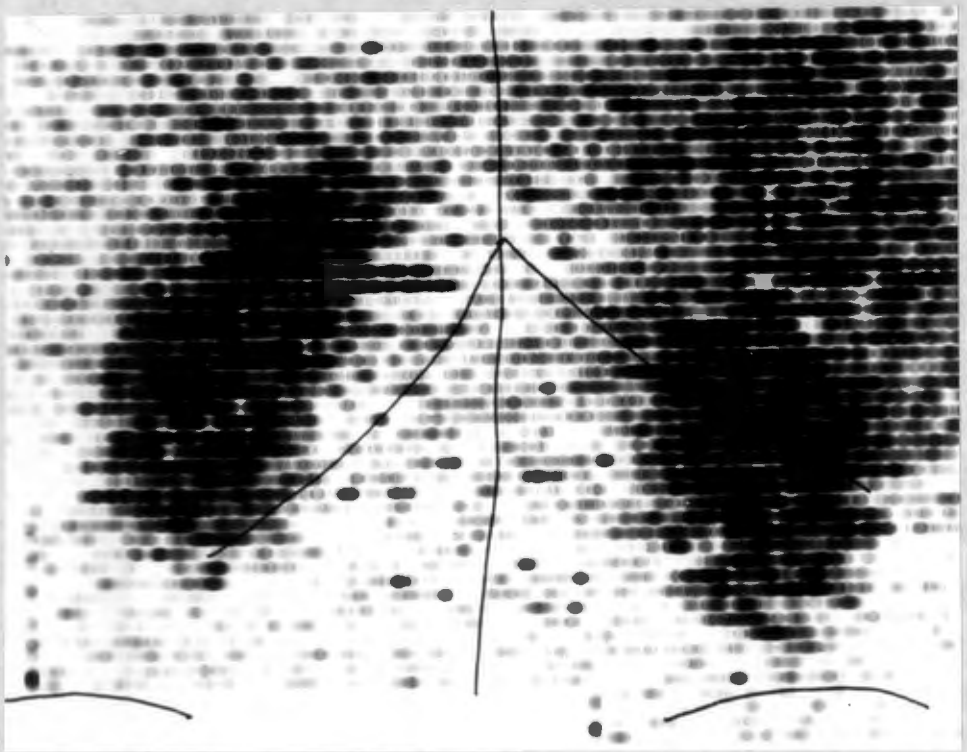

Fig.4.6: ^{75}Se - DLmeso - selenocystine. Posterior scan performed on the same patient as in Fig.4.5. The black lines represent the surface markings of the vertebral spines, 12th ribs and iliac crests. The scan demonstrates the strong renogram effect. Page 151 .

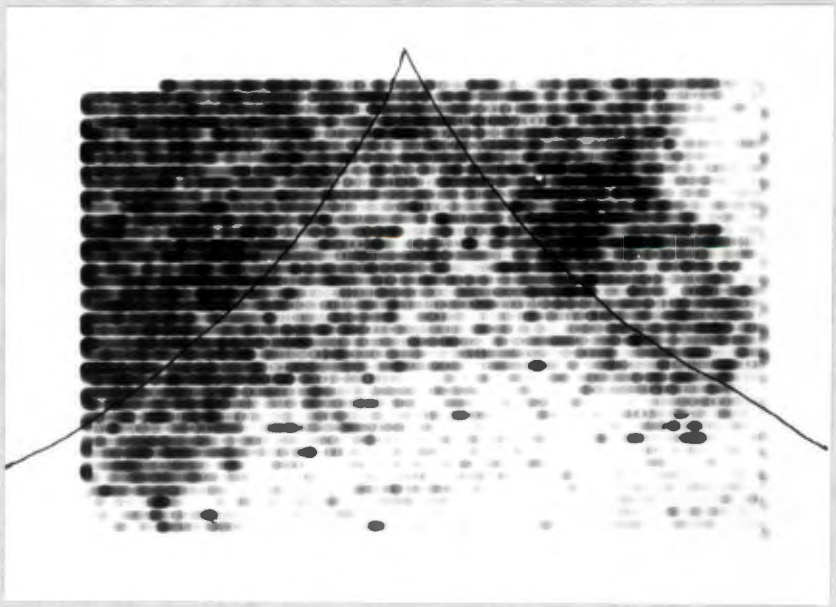

Fig.4.7: ^{75}Se - DL-mese - selenocystine: Five hour scan performed on the same patient as in Fig.4.5. Page 151.

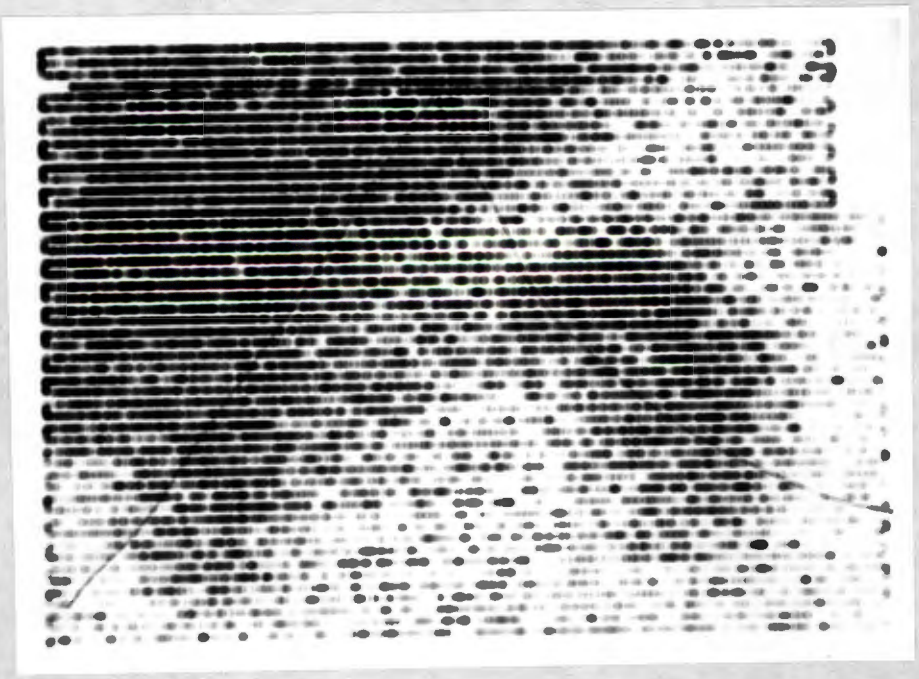

Fig.4.8: ^{75}Se - L - selenocystine: Human abdominal scan commenced 30 minutes after the isotope injection. Page 151 .

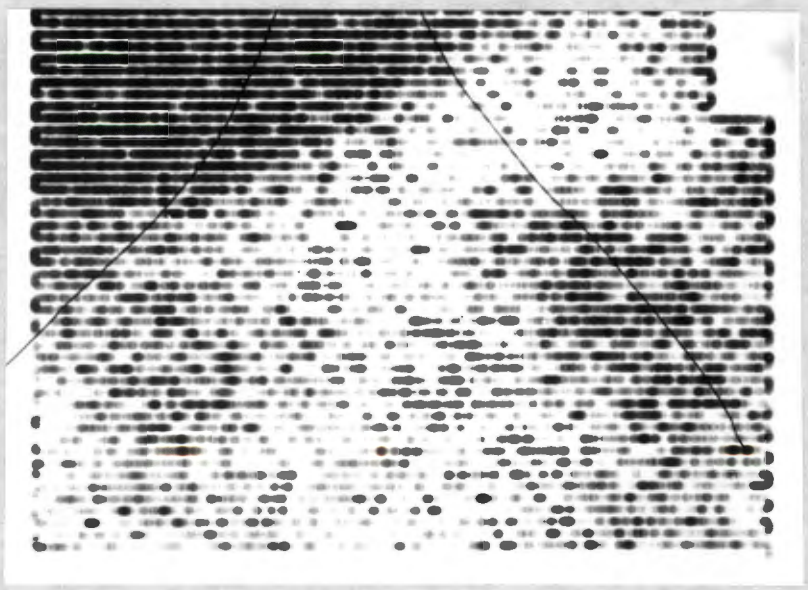

Fig.4.9: ^{75}Se - L - selenocyttines Scan performed at 5 days on the same patient as in Fig.4.8. Page 151.

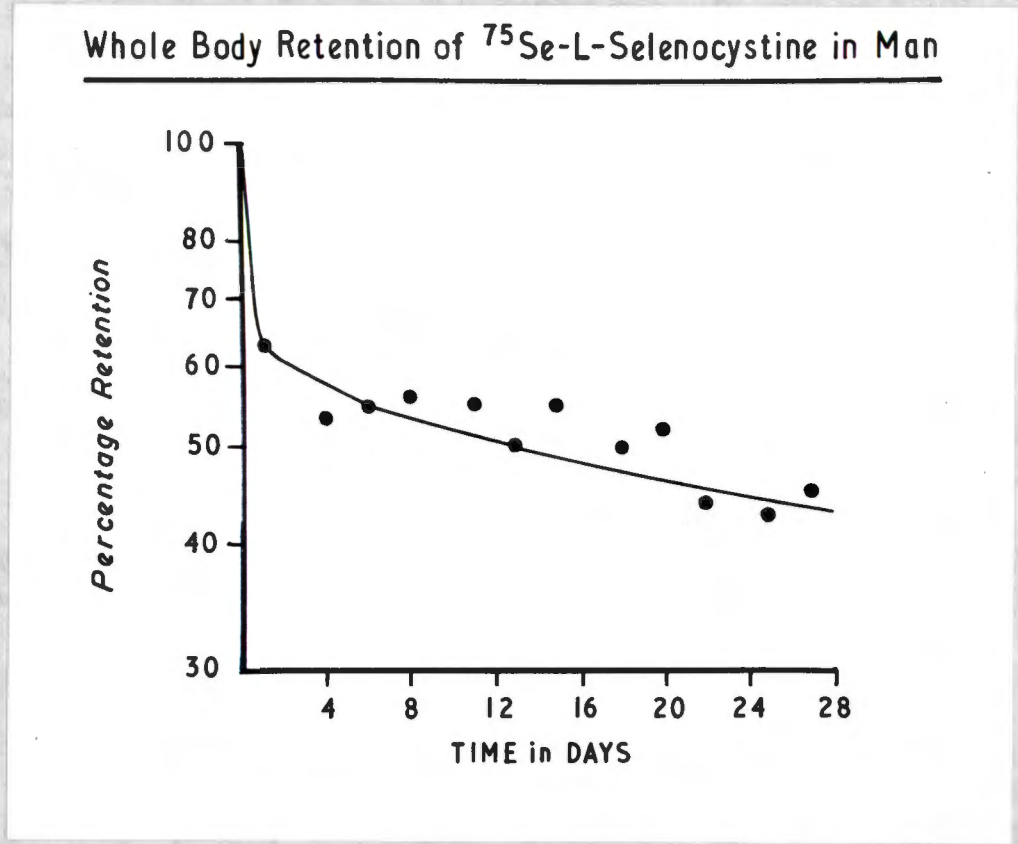
Whole Body Retention of ^{75}Se-L-Selenocystine in Man
Percentage Retention
100
80
70
60
50
40
30
4
8
12
16
20
24
28
TIME in DAYS

Fig.4.10:

Whole-Body Retention of ^{75}Se - L - Selenocystine

Whole-body counting of the patient injected with ^{75}Se-L - selenocystine showed an initial rapid reduction of activity with 65% retention after 24 hours and a half-life of 13 days (Fig.4.10).

Part 4. Interpretation of Results

Animal Studies

i) Whole-Body Isotope Retention

There is a striking reduction in whole body activity by 24 hours in the rabbits injected with the ^{75}Se - selenocystine compounds. This implies the excretion of approximately 50% of injected ^{75}Se - selenocystine as compared to 10% of ^{75}Se - selenomethionine within the first 24 hours after injection.

It is noted that the mean retention of ^{75}Se - L - selenocystine (59%) is greater than that of the ^{75}Se - DLmeso - selenocystine (40%). This probably reflects the better tissue utilization of the naturally occurring form of the selenoamino acid.

ii) Abdominal Scans

In the ^{75}Se - L - selenomethionine scans, the increased visceral uptake at 5 hours presumably reflects the clearance of circulating isotope from the blood stream. The activity in the kidneys and bladder indicates the loss of some of the original isotope through the urinary system.

The ^{75}Se - DLmeso - selenocystine scans, particularly when compared to ^{75}Se - selenomethionine, suggest rapid renal clearance and generally poor tissue utilization of the injected isotope.

The scans of ^{75}Se - L - selenocystine appear intermediate to those of the preceding two selenoamino acids:-

i) There is considerably more urinary tract activity in these rabbits than in those injected with ^{75}Se - L - selenomethionine. This probably reflects a much greater urinary excretion of isotope;

ii) There is generally less background activity in the 5 hour scan as compared to the ^{75}Se - selenomethionine, reflecting less bowel utilization of the ^{75}Se - L - selenocystine. However background activity is higher with the L - form than with the DLmeso - form of selenocystine. This presumably reflects better tissue utilization of the naturally occurring form of the selenoamino acid.

iii) Organ Distribution of Injected Isotope

This study confirmed the impression of isotope distribution obtained from the scans. Besides the liver, uptake in the pancreas, small bowel and stomach is relatively high with ^{75}Se - L - selenomethionine. With ^{75}Se - L - selenocystine renal activity is much more impressive and stomach, small bowel and pancreas uptake relatively low.

Human Studies

The behaviour of ^{75}Se - selenocystine in humans was similar to that in rabbits i.e. a significant fraction of the injected dose is rapidly cleared by the kidney. This is associated with a strong renogram effect on the scan. In none of the three patients scanned was the pancreatic image particularly strong.

This more rapid renal clearance of ^{75}Se - L - selenocystine is reflected in the half-life of 13 days as determined by whole-body counting.

Part 5. Discussion

The behaviour of selenocystine in man is similar to that in rabbits and is characterised by the rapid renal clearance and excretion of a significant proportion of the intravenously injected dose. The prominent renogram effect would tend in man to hinder satisfactory interpretation of the pancreatic scan as in all three scans the tail of the pancreas overlapped the upper pole of the left kidney. As this anatomical relationship is a constant one, it could only add to the problems of scan interpretation.

It seems unlikely that the pancreatic image can ever be as satisfactory with selenocystine as it is with selenomethionine. If hepatic total and specific activity are greater than that of pancreas (assuming the rabbit results can be extrapolated to humans), then calibration of the scanning machine over a hot-spot in the liver would tend to minimize pancreatic activity and the pancreas would show up poorly on the scan. Furthermore any increase in ^{75}Se - selenocystine dosage to improve the quality of the pancreatic scan (the radiation effect being offset by the more rapid excretion), would be associated with a concomitant increase in renal activity as well.

The behaviour of systemically injected selenocystine appears to be similar to that of the parent amino-acid cystine. Blum (1904) noted that injection of cystine into the peripheral vein of dogs resulted in a large amount of cystine being excreted with the urine, with the formation of cystine crystals. Steams and Lewis (1930) confirmed these findings by injecting cystine into rabbits.

The behaviour of the different configurations of selenocystine used in the experiments described, confirms that this factor is of particular importance when considering the metabolism of these compounds. Both the whole-

Table 4.3

ORGAN ACTIVITY IN RABBIT SEVEN DAYS AFTER ISOTOPE INJECTION

Organ	^{75}Se - L - Selenomethionine		^{75}Se - L - Selenocystine	
	% Dose Gm. Tissue	% Total Dose in Organ	% Dose Gm. Tissue	% Total Dose in Organ
Pancreas	0.05	0.34	0.01	0.05
Liver	0.09	7.62	0.13	8.02
Small Bowel	0.02	0.62	0.02	0.51
Stomach	0.04	0.67	0.03	0.41
Kidneys	0.12	1.67	0.18	1.78
Spleen	0.05	0.04	0.05	0.03
Gonads	0.04	0.05	0.04	0.04
Heart	0.03	0.15	0.03	0.13

body retention studies and the pancreatic scans in the rabbits suggested that L - selenocystine was better retained and presumably better utilized by a larger number of organs than was the DLmeso-selenocystine. The larger renal excretion of the filtered DLmeso - selenocystine would suggest that the configuration of selenocystine is also important for transport of the selenoamino acids by the renal tubule. This observation is considered to be valid as the trace quantities of selenocystine used in these experiments are unlikely to have flooded the absorptive capacity of the renal tubules.

In a study comparing the fate of injected ^{75}Se - selenomethionine and ^{75}Se - selenocystine in rats, Anghileri and Marques (1965) reported that both selenoamino acids show a similar pattern of visceral incorporation. Throughout the 7 days of their study the activity primarily incorporated into the liver remained steady, but in other organs it decreased with the exception of the testes which showed a "considerable" increase throughout the course of the experiment (both for selenomethionine and for selenocystine). Observations of the tissue levels of the injected selenoamino acids in rabbits at 7 days (Table 4.3) shows a fall in all organ activity as compared to the 1 hour level (Table 4.2). The general difference in results as compared to the rat studies may well reflect a species difference in the metabolism of these compounds. However, the rat tends to be coprophagic unless deliberately prevented. Anghileri and Marques do not mention measures to prevent coprophagy and in such studies this could be an important factor in the recycling of excreted isotope.

Part 6. Conclusions

Neither ^{75}Se - L - nor ^{75}Se - DLmeso - selenocystine offer any advantage over ^{75}Se - L - selenomethionine as pancreatic scanning agents. Because of the additional problem of renal overlap they are much less satisfactory agents.

From the whole-body retention studies and abdominal scans in rabbits it appears that tissue utilisation of the natural L - configuration of selenocystine is greater than that of the DLmeso - form. Because of the larger fraction of injected DLmeso - selenocystine lost in the urine it is likely that renal tubular transport is also influenced by the configuration of the compound.

Selenocystine injected via a peripheral vein behaves in a similar fashion to cystine in that a relatively large proportion of the dose is rapidly cleared and excreted by the kidneys.

CHAPTER 5

ATTEMPTS TO POTENTIATE

^{75}Se - SELENOMETHIONINE UPTAKE

BY THE PANCREAS

The two main advantages which are likely to result from potentiating pancreatic selenomethionine uptake would be to simplify the reading of the pancreatic scan and to increase its diagnostic accuracy. There have been three main approaches to this problem. Firstly there have been attempts to stimulate protein synthesis by the pancreas to increase amino - acid uptake. Secondly, increasing the pancreatic blood flow would present a larger fraction of the pulse injection of ^{75}Se - selenomethionine to the pancreas for utilization. Thirdly, retarding the release of synthesized protein may potentiate the scan appearance. This last possibility implies the assumption that secretion of ^{75}Se - selenomethionine containing enzymes occurs before completion of the scan and that this results in loss of activity in the pancreas.

Attempts have been made to stimulate pancreatic protein synthesis and blood flow in order to enhance uptake of the radioactive label. Methods used include a high protein feed (Blau, 1964; Haynie, Svoboda and Zuidema, 1964; Burke and Goldstein, 1964; Diethelm and Haacke, 1965; Sodee, 1964; Rodriguez - Antunez, Filson, Sullivan and Brown, 1966; Van Vaerenburgh, Van Vaerenburgh, Demeulenaere, Yvergneaux and Barbier, 1966; King, Sharpe, Grubb, Brock and Greenberg, 1966; Centi Colella and Pigorini, 1967; Laconi, Melfi, Cataliotti and Semilia, 1965); pancreozymin - secretin injections (Blau, 1964; Haynie, Svoboda and Zuidema, 1964; Beierwaltes, 1964; Diethelm and Haacke, 1965) and amino - acid infusions (Tabern, Keamey and Dolbow, 1965). None of these have proved successful.

Likewise, attempts to delay the secretion of the formed enzymes by morphine or probanthine injections have not improved the quality of the pancreatic scan (Rodriguez - Antunez, 1964; Diethelm and Haacke, 1965; Tabern, Keamey and Dolbow, 1965; Van Vaerenburgh, Van Vaerenburgh, Demeulenaere, Yvergneaux and Barbier, 1966).

In keeping with the experience of Burdine and Haynie (1965), Lahdevirta and Haikonen (1965), Sodee (1965), Kaplan, Ben - Porath, Fink, Clayton and Jacobson (1966), Centi Colella and Pigorini (1967) and Kakehi, Tateno, Uchiyama and Tsuchiya (1967) special preparatory techniques were not used in the majority of patients in the study reported in Chapter 3. However, the patients were encouraged to take as complete a diet as possible for the few days preceding the scan and where possible, a large breakfast on the morning of the scan. The impression was gained that in general the quantity of food consumed prior to scanning did not greatly influence the quality of the scan. This applied too to the first 15 patients of the series to whom a supplementary drink of protein concentrate of 20 to 40 gm. had been given 1 to 1½ hours prior to the ^{75}Se - selenomethionine injection.

The search for an agent which could increase pancreatic ^{75}Se - selenomethionine uptake and so improve the quality of the scan led to a review of the effects of the naturally occurring trypsin inhibitors on the pancreas.

Part 1. The Effects of the Naturally Occurring Trypsin Inhibitors on the Pancreas

Since 1948 (Chemick, Lepkovsky and Chaikoff) it has been known that chickens fed on raw soybean meal develop large pancreases with an increased protease content. In 1960, Booth, Robbins, Ribelin and Deeds studied the heart, lungs, thyrpid, testes, spleen, liver, pancreas, kidney, adrenals and intestine of rats fed a control diet and one supplemented with raw soybean meal. All organs were found to be normal except the pancreases of animals fed raw soybean meal. In these the acinar cells were considerably hypertrophied and packed with zymogen content. This histological impression of acinar hypertrpphy was corroborated in chickens fed raw soybean meal by Saxena, Jensen, McGinnis and Lauber (1963). These observations received biochemical confirmation in a study by Konijn and Guggenheim (1967) who demonstrated an increased ribonucleic acid (R.N.A.) content in the pancreas of rats fed raw soybean meal. The deoxyribonucleic acid (D.N.A.) content of the raw soybean fed animals was similar to that of controls but the D.N.A. concentration per gland was significantly less, suggesting that the pancreatic enlargement was due to a true hypertrophy rather than a hyperplasia of the cells. The increased R.N.A. content of the pancreas in the raw soybean fed rats was in keeping with the greater protein synthesizing capacity of these pancreases.

In 1961, Haynes and Lyman implicated the trypsin inhibitor in raw soybean meal as a pancreatic stimulator resulting in the excessive formation of pancreatic enzymes with the subsequent loss of critical amounts of limiting amino - acids in the faeces. In this way they could explain the enlarged pancreas, poor growth and large faecal nitrogen excretion noted in rats or chickens fed on large supplements of raw soybean. This hypothesis was supported by the observation of Booth, Robbins, Ribelin and De Eds (1960) that the addition of the 4 amino - acids, threonine, valine, methionine and tyrosine to a raw soybean diet, corrected the poor growth and reduced food efficiency but did not prevent pancreatic hypertrophy. In 1963, Rackis, Smith, Nash, Robbins and Booth showed that the greatest inhibition of rat growth and enlargement of

the pancreas occurred with meal fractions possessing very high trypsin - inhibitor activity. Meal fractions possessing low trypsin inhibitor activity inhibited growth and caused pancreatic enlargement to a lesser degree.

In studying the effects of the naturally occurring trypsin inhibitors on the mammalian pancreas Melmed and Bouchier (1968) demonstrated that a low dietary supplement of the purified trypsin inhibitors from a variety of sources (soybean, ovomucoid and bovine pancreas respectively) are powerful inducers of amylase synthesis (Table 5. I) and therefore presumeably of the other digestive enzymes as well, in the rat pancreas.

Lyman and Lepkovsky (1957) and Lyman, Wilcox and Monsen (1962) have shown that a single supplement of the purified trypsin inhibitor to the diet in rats is capable of stimulating an exaggerated secretion of digestive enzymes from the pancreas to the bowel lumen. The results of these experiments suggested that the purified trypsin inhibitor is capable of exerting an acute effect on the pancreas via the bowel lumen. In view of its potential for actually inducing pancreatic enzyme synthesis as measured after a few days of feeding, it seemed likely that the inhibitor was capable of stimulating enzyme synthesis and secretion after a single dose. The pancreatic enlargement which occurs being a manifestation of repeated stimuli. For these reasons it was decided to assess the effects of a dose of the purified soybean trypsin inhibitor on the scan appearance.

Table 5.1 .

INFLUENCE OF TRYPSIN INHIBITOR ON THE AMYLASE CONTENT OF THE RAT PANCREAS

(MELMED and BOUCHIER, 1968)

Group	Inhibitor Content of Diet (%)	Amylase u ($x10^3$) mg. Protein	Amylase u ($x10^3$) Pancreas
Control	0	10 (± 3)	951 (± 266)
Soybean	0.6	38 (± 3)	4,.824 (± 746)
Ovomucoid	0.6	28 (± 11)	3, 072 (± 911)
Bovine Pancreas	0.013	23 (± 9)	3, 400 (± 1,306)

Part 2. Aims of Study

The aims of this study were twofold:- Firstly, to assess whether a preparatory dose of the purified soybean trypsin inhibitor potentiated ^{75}Se - selenomethionine uptake by the human pancreas; and secondly, to assess whether this enhancement of the pancreatic scan, if it occurred, improved the diagnostic quality of the scan.

Part 3. Material and Methods

Sixty consecutive patients requiring pancreatic scans were chosen for inclusion in this study. Their classification according to the presence or absence of pancreatic disease is presented in Table 5.2 .below:-

Table 5.2

Clinical Diagnosis of the Pancreatic State in the 60 Patients of this Study.

Normal	24
Pancreatic Carcinoma	12
Acute Pancreatitis	7
Chronic Pancreatitis	9
Miscellaneous (Diabetes Mellitus, gastroenterostomy, etc.)	8
Total	60

None of these patients are included in the study presented in Chapter 3. The state of the pancreas was determined clinically by a variety of biochemical and radiological procedures and in some cases at laparotomy.

In order to ensure a meaningful assessment, the administration of the purified soybean trypsin inhibitor and the supervision of the scan was attended to by a single colleague who maintained a consistent preparatory protocol in all the patients.

The purified soybean trypsin inhibitor was obtained commercially (Serevac Laboratories (PTY)Ltd., Maidenhead, Berks, England) in bulk and transferred in 50 mg. amounts to gelatin capsules for administration.

The patient preparation was identical to that described in Chapter 3 but in 30 of the 60 patients in this study 200 mgs. (4 capsules) of the purified trypsin inhibitor was given 1 to 1½ hours before the ^{75}Se - selenomethionine injection. In the order in which the scans were performed this was from patients number 11 to 40.

The scans were viewed at the end of the study by the author in a single session, without knowledge of any clinical detail or whether the patient had received purified trypsin inhibitor. Three observations were recorded for each scan viewed:-

(i) The quality of the pancreatic impression i.e. whether excellent, good, fair or poor;

(ii) Whether the patient was likely to have had trypsin inhibitor (assuming it to potentiate the ^{75}Se - selenomethionine uptake) and

(iii) Whether the scan was normal or abnormal.

Part 4. Results

It was impossible to anticipate which patients had received purified soybean trypsin inhibitor on the quality of the scan appearance. Of the 30 patients who had received trypsin inhibitor only 11 patients were predicted as having had it. Seventeen patients out of the 30 in the control group were predicted to have had it when in fact they had not.

There were 6 errors in diagnosis in the group of 60 patients, all amongst patients who were thought to have pancreatic disease clinically, but in whom the pancreas was passed as normal on the scan. One of this group was thought to have a carcinoma, the others to be suffering from acute or chronic pancreatitis.

Part 5. Discussion

This controlled study indicates that under the conditions described a single dose of 200 mgs. soybean trypsin inhibitor does not influence the ^{75}Se - selenomethionine uptake by the pancreas. The quality of the better pancreatic scans in both groups (Figs.5.1 and 5.2 .) is comparable and it was found impossible to predict which patients had received the trypsin inhibitor capsules. As might be expected from this result the diagnostic accuracy was not influenced by whether or not the patient had received trypsin inhibitor.

The overall accuracy of the scan reporting was 90% as there were 6 errors out of 60 scans. The mistakes were all made in the group of patients thought to have pancreatic disease clinically. However, it could not be sure that at the time of the scan pancreatic morphology and function was not in fact normal.

The available experimental evidence suggests that the naturally occurring trypsin inhibitors are powerful inducers of the pancreatic digestive enzymes. It is not yet determined whether humans can respond to these substances as do rats or chickens. However the basic anatomical and functional similarities in the relationships of the upper gastro-intestinal organs and in the ultra - structure of the pancreatic exocrine cell in a wide variety of avian and mammalian species (Caro and Palade, 1964) makes it likely that under the correct conditions they will respond similarly.

There are three factors which may account for the negative results obtained in this study. Firstly, the quantity of trypsin inhibitor used may have been insufficient. The dose of 200 mgs. was arbitrarily chosen but the choice was primarily influenced by the potency of the compound demonstrated in rat experiments (Table 5.1). Five to 10 times this amount may be a more realistic dose in humans. Secondly, the timing of the ^{75}Se - selenomethionine

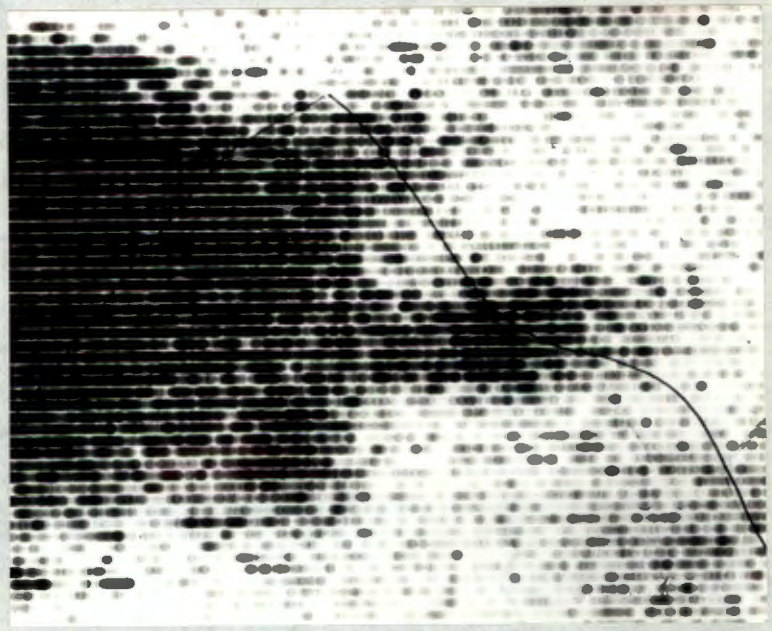

Fig.5.1: A ^{75}Se - L - selenomethionine photoscan of the abdomen in a patient who had not received a dose of purified soybean trypsin inhibitor. Isotope uptake is excellent and the gland appears normal. The head of the pancreas is contiguous with but is not overlapped by the liver edge. Page 183.

Fig.5.2: A ^{75}Se - L - selenomethionine photoscan of the abdomen in a patient who received 200 mgs. of purified soybean trypsin inhibitor orally, 1½ hours before the isotope injection. Isotope uptake throughout the gland appears excellent. There is an area of "physiological" thinning between the head and tail of the pancreas. The head of the pancreas is only marginally overlapped by the right lobe of the liver. The quality of isotope uptake in this scan is comparable to that shown in Fig.5.1.

injection in relation to the preceding dose of trypsin inhibitor may not have been optimal. For example, in rats, maximum output of pancreatic enzymes occurs 3 to 6 hours after ingesting a diet supplemented by the soybean trypsin inhibitor (Lyman and Lepkovsky, 1957[5]). Therefore, it may be more realistic to give the ^{75}Se - selenomethionine injection 3 to 6 hours after the trypsin inhibitor instead of the 1 to 1½ hours chosen for this study. Finally, it may only be possible to demonstrate the effects of the naturally occurring trypsin inhibitor on the human pancreas after having increased the enzyme capacity of the pancreas by a suitable period of treatment with the inhibitor prior to scanning. Siegel, Jacobs, Studer and Potchen (1968) have shown in rats that an 8 day raw soybean diet augments the selenomethionine uptake by the rat pancreas twofold. If the ingestion of trypsin inhibitor does induce the synthesis of digestive enzymes in the human pancreas, this approach would provide a rational solution to the problem of enhancement of the pancreatic scan.

Part 6. Conclusions

Measures such as supplementary protein feeding, secretin - pancreozymin injections, amino - acid infusions, and morphine and probanthine injections have all failed to produce a convincing improvement in the quality of the pancreatic scan.

Dietary supplements of raw soybean meal or the purifed trypsin inhibitor from a variety of biological sources such as soybean, ovomucoid or bovine pancreas, have been shown to be powerful inducers of pancreatic digestive enzyme synthesis in rats and chickens.

A controlled trial has been undertaken to assess the effect of a single orally administered 200 mg. dose of purified soybean trypsin inhibitor on the pancreatic scan. It was concluded that under the conditions of this trial the trypsin inhibitor was without effect.

In view of the failure of all preparatory techniques reported to enhance ^{75}Se - selenomethionine uptake by the pancreas it is suggested that a rational approach to the problem would be through the induction of the pancreatic digestive enzymes by the continued administration of trypsin inhibitor for a period prior to performing the pancreatic scan.

CHAPTER 6

CONCLUSIONS

The advent of a technique which may demonstrate the condition of the whole pancreas with minimal discomfort to the patient is a significant advance on the available techniques of pancreatic investigation. From the patient's point of view a pancreatic scan may avoid the discomfort of a preparatory fast, deodenal intubation or arterial puncture. The relative ease with which a pancreatic scan may be performed in any patient, particularly the sick, the aged and the anxious is probably its most outstanding advantage.

It is difficult to compare the clinical value of the available techniques for pancreatic diagnosis primarily because of the widely differing conditions under which most reported studies have been conducted. The best established of the available pancreatic function tests is that described by Dreiling and Janowitz (1962) and involves the duodenal aspiration of pancreatic juice secreted in response to secretin and pancreozymin injection. While of value in establishing a diagnosis of chronic pancreatic insufficiency or carcinoma of the head of pancreas diagnosis of more distal lesions in the body of the pancreas is generally poor with this technique. According to Dreiling and Janowitz the diagnostic accuracy in carcinoma of the pancreas falls from 95% in the head to 3% in the tail.

Cytological techniques in practised hands may also be of value. Raskin, Wenger, Sklar and Pleticka (1958) used cytological examination of secretin stimulated duodenal juice to make a correct diagnosis in 21 (63%) of 34 patients with pancreatic cancer. Combining a secretin function test with cytological examination of the aspirated fluid may improve the diagnostic value of both tests considerably. In 60 patients with proven pancreatic carcinoma studied by Dreiling, Nieburgs and Janowitz (1960) 47 had positive cytology and 43 a positive (pathological) secretin test. Considering both tests together 56 (95%) of the 60 patients were correctly diagnosed. Wegner and Raskin (1958) could establish the correct diagnosis in 89% of 35 patients with pan-

creatic carcinoma using both cytology and the secretin stimulation test. Assessed independently, the secretin test was abnormal in 75% and cytology in 62% of the patients.

Of the radiological techniques available, barium meal is widely used to screen patients for the presence of pancreatic carcinoma. The limitations of this technique in the diagnosis of pancreatic disease have been discussed in Chapter 1. Besides the fact that the growth must be fairly large in order to be apparent, the signs are mostlt indirect and non - specific. Like the secretin stimulation test the diagnostic accuracy diminishes from the head to the tail of the pancreas. In a retrospective survey of the routine interpretation of barium studies of the upper gastro - intestinal tract in 100 patients with proven pancreatic carcinoma (67 of the head, 26 of the body and 7 of the tail), Eyler, Clark and Rian (1962) found only 24 cases in whom a positive diagnosis had been made. In a controlled retrospective review of the same series by these authors, a positive diagnosis of "pancreatic enlargement" could only be made in 57 of the 100 cases studied. A comparative evaluation of the efficacy of arteriography in demonstrating pancreatic lesions is very difficult to determine. Patients undergoing arteriography are a highly selected group in whom the clinical suspicion of neoplasia is usually very high. Because of the practical difficulties it is very difficult to embark on a prospective survey in order to establish its value as a diagnostic procedure in pancreatic disease. In experienced hands it is of undoubted value. In a limited study of 25 patients suffering from abdominal pain of obscure cause Meaney, Winkelman, Sullivan and Brown (1963) found 3 patients with arteriographic abnormalities thought to be due to pancreatic carcinoma. The diagnosis was confirmed in all 3 patients at laparotomy. Baum, Roy A Finkelstein and Blakemore (1965) stress that the use of selective arteriography may be of particular value in selected patients, such as in those thought to be suffering from insulinoma in particular. These tumours

have a rich vascularity and may be revealed by the "tumour blush". However Baum, Roy, Finkelstein and Blakemore consider that in view of the lack of vascularity in the majority of carcinomas of the pancreas and the fact that the lesions must be of considerable size to cause recognisable vascular displacements, they do not feel optimistic about diagnosis of early pancreatic carcinoma by angiography.

Considering the larger reported series of pancreatic scans in patients with pancreatic carcinoma, Sodee (1966) claimed a diagnostic accuracy of 96% in 26 patients. Brown, Sircus, Smith, Donaldson, Dymock, Falconer and Small (1968) reported the correct diagnosis in 93% of 14 patients. The worst result reported is that of Rodriguez - Antunez, Filson, Sullivan and Brown (1966) who diagnosed 41 patients as having carcinoma of the pancreas on the photoscan. These authors could subsequently only confirm 27 of the 41 "positive" scans i.e. they had 34% false positives. In addition they missed 4 patients with carcinoma whom they thought were normal. The report by these authors suggests a general lack of appreciation of all the variations of the normal and abnormal pancreatic scan. This state of affairs is very likely to lead to an over-diagnosis of pancreatic disease such as cancer. In the studies reported in this thesis, of the 100 patients' scans viewed without any knowledge of the clinical details (40 patients reported in Chapter 3 and 60 in Chapter 5), 10 were shown at laparotomy to have carcinoma. In 8 of these 10 patients, the diagnosis was correctly made on the appearance of the scan alone. Pancreatic scanning compares favourably in diagnostic accuracy with the available techniques for the diagnosis of pancreatic carcinoma. With due considerationsof its limitations, it is likely that ^{75}Se - selenomethionine pancreatic scanning will become a valuable screening technique in helping the clinician to decide whether or not any patient has serious underlying pancreatic disease and in particular, carcinoma.

Like the more specialised radiological procedures which require costlier equipment, the newer scanning machines are also expensive. In addition the price of ^{75}Se - selenomethionine is at present £40/mCi (The Radiochemical Centre, Amersham) in Britain. This averages approximately £10 per patient in the cost of the isotope alone. It would seem that the expertise required for the most accurate interpretation of the pancreatic scan is similar to that of the radiologist interpreting a pancreatic angiogram. In both cases it is dependant on a proper appreciation of the variations of the normal and the manner in which a variety of diseases may influence this pattern. Like most specialised procedures therefore, the maximum information will be obtained from those units in which pancreatic scanning is performed as a regular service. In this way the cost of the scan and its potential hazards (radiation effects) will be well offset by the information it is likely to reveal concerning the state of the patients pancreas.

APPENDIX 1.

ILLUSTRATIVE CASE HISTORIES

Normal Pancreas

Patient No.1: A 51 year old woman who was admitted for the investigation of recurrent epigastric discomfort over 6 months. The discomfort was unrelated to meals and did not wake her up at night. She also complained of anorexia and the loss of 10 pounds in weight in the 3 months prior to admission. Besides appearing depressed the patient was quite normal on clinical examination. In particular, there was no visceromegaly or masses detectable on physical examination. The blood count was normal as were the blood urea, liver function tests, serum amylase, proteins and fasting blood sugar. X-ray of chest, cholecystogram and barium meal were all quite normal. A ^{75}Se - selenomethionine scan revealed a normal pancreas with excellent isotope uptake throughout the gland (Fig.3.6). The patient was diagnosed as suffering from depression. She was treated with amitryptylline and made an excellent recovery with prompt disappearance of the symptoms. She regained the weight lost over 3 months and appeared in excellent health one year later on a follow-up examination, 6 months after discontinuing the tablets.

Patient No.2: A 34 year old woman who was investigated for recurrent abdominal pain. A gastric ulcer was eventually diagnosed and the patient was submitted to partial gastrectomy. The pancreas was carefully inspected and found to be normal (Fig.3.5).

Patient No.3: A 38 year - old man in whom a pancreatic scan was performed in investigation of periodic epigastric discomfort. Clinical examination, blood count and barium meal were all normal. The patient was reassured and discharged remaining quite well over 18 months on follow-up examination. (Fig. 3.8)

Patient No.4: A 75 year - old woman who had become jaundiced one month before admission. She had no abdominal pain and suffered no pruritis. There

was no change in bowel habits though her stools had become pale and the urine darker since the onset of the jaundice. Clinically, the patient was apyrexial and there were no stigmata of chronic liver disease or portal hypertension. On abdominal examination, the liver was 3 cms. enlarged and slightly tender. There was no splenomegaly. The serum bilirubin 8 mgs/100 ml. (conjugated 7 mg./100 ml.); alkaline phosphatase 60 K.A units/100 ml.; aspartase transaminase 27 i.u./l ; cholesterol 590 mgs./100 ml.; increased x_2 globulin on serum electrophoresis. Barium meal was normal and the pancreatic scan showed a normal pancreas of unusual configurations (Fig.3.7). The jaundice faded throughout her admission and within 3 weeks the total serum bilirubin had fallen to 3.0 mgs./100 ml. Two months after discharge the patient was anicteric with a total serum bilirubin of 1.2 mgs./100 ml. The clinical diagnosis was cholestatic hepatitis though cholelithiasis could not be excluded. There was no history of drug ingestion.

Carcinoma of the Pancreas

Patient No.5: (Fig.3.11). A 72 year - old man who gave a 7 week history of malaise, anorexia, loss of weight and increasing jaundice. Clinically it was not possible to palpate a gallbladder. The serum bilirubin was 25 mg./100 ml. (conjugated bilirubin 19.5 mg./100 ml.) and the alkaline phosphatase was 65 K.A. units/100 ml. A barium meal showed a duodenal ulcer. The duodenal loop appeared normal. At laparotomy a 3 cm. diameter carcinoma was detected as depicted on the scan.

Patient No.6: (Fig.3.12). A 52 year - old man with a 9 month history of low backache which was followed by 3 months epigastric pain. Four weeks before admission the patient developed jaundice with pale stools and dark urine. On physical examination there was no visceromegaly or masses detected in the abdomen. The serum bilirubin was 5.6 mg./100 ml. (conjugated bilirubin 4.0 mg./100 ml.) and the alkaline phosphatase was 40 K.A.units/100 ml.. A laparotomy revealed a large carcinoma of the pancreas involving the head, neck and body and extending into the portal vein.

Patient No.7: This 36 year - old woman had suffered backache in the region of the 1st. lumbar vertebra for 2 years. For 5 months before admission it had radiated round both subcostal regions and for 2 months it had been particularly intractable and severe. Clinically the patient was a frail woman who appeared depressed and in pain. A hard immoveable mass was palpated in the epigastrum. The serum alkaline phosphatase was 33 K.A.units/100 ml. The serum amylase, bilirubin blood sugar, cholesterol and protein estimations were all normal. A barium meal showed some flattening of the medial margin of the second part of the duodenum. The pancreatic scan (Fig.3.13) was suggestive of carcinoma of the body of the pancreas. This was confirmed at laparotomy by biopsy as the lesion was unresectable.

Zollinger - Ellison Syndrome

Patient No.8: A 52 year - old male with a 6 year history of recurrent bouts of epigastric pain lasting up to 3 days and unrelated to food, alcohol or posture. For about the same period he had diarrhoea of varying severity, the stools being pale and watery. Four years previous to admission a diagnosis of "Jejunitis" had been made on the basis of a barium meal. Clinically the patient was thin with the signs of chronic bronchitis and emphysema. No visceromegaly or masses were detected on abdominal examination. The faecal fat level varied between 14 to 26 g per day. The serum alkaline phosphatase was 29 K.A.units/ 100 ml. but there was no evidence of Pagets disease. The oral glucose tolerance test using a standard 50 g glucose load showed moderate impairment with levels of 90, 180, 190, 120, 100 mg./100 ml. at zero, 30, 60, 90 and 120 minutes respectively. The serum amylase, calcium, phosphorus, urea, electrolytes and protein were all normal. A secretin stimulation test (1 u/kg. Boots secretin intravenously) gave a volume output of 2.2 ml./kg. body weight and a bicarbonate content of 17 mEq./l. An augmented Histalog test (2 mg./kg. body weight) showed a basal acid secretion of 24 mEq./hour and a maximum response of 50 mEq./hour. Jejunal biopsy showed a normal mucosal morphology. The patient was diagnosed as having the Zollinger - Ellison syndrome and chronic pancreatitis. At laparotomy a small 1 cm. diameter nodule was felt in the tail of the pancreas. A two-thirds distal pancreatectomy was performed. On sectioning the nodule proved to be a small cyst but histology of the surrounding tissue showed considerable coarse and fine fibrosis with distortion of many of the ducts. Small groups of carcinoma cells in clumps and lines as well as single cells were present within the fibrous tissue. On the basis of their staining properties these carcinoma cells were thought to be derived from the α- cells of pancreatic islets.

A Histalog test repeated 25 days after the operation showed a basal acid output of 5 mEq./hour. The faecal fat had decreased to 8 g per day on a normal diet and there was no diarrhoea. A repeat scan 4 months after the operation showed complete disappearance of the area of increased uptake (Fig.3.144). No gastrin-like activity could be demonstrated on an extract of the tumour tissue.

Acute Pancreatitis:

Patient No.9: A 76 year - old man who in 1966 underwent laparotomy for a severe bout of sudden abdominal pain and was found to be suffering from acute pancreatitis. His blood amylase postoperatively was 10,600 u/100 ml.. A cholecystectomy was performed at this operation because of the presence of gall-stones. A pancreatic scan was performed 10 days postoperatively (Fig.3.10a). The patient was rescanned 10 months later after full clinical recovery and no further attacks (Fig.3.10b).

Patient No.10: A 25 year - old man with a 7 week history of deepening jaundice with pale stools and dark urine. At the onset of this illness the patient had recurrent bouts of upper abdominal pain associated with anorexia and malaise. Clinically he was mildly icteric. The liver edge was palpable in the epigastrum. Biochemical investigation and liver biopsy suggested large-duct obstruction and because of an exacerbation of the abdominal pain a laparotomy was performed. At operation the duct system was dilated. This was due to a gallstone impacted at the Ampulla of Vater. The pancreas head was swollen and inflamed. The stone was removed via a sphincterotomy, a cholecystectomy was performed and the patient made an excellent postoperative recovery. (Fig. 3.15)

Patient No.11: A 34 year - old man who had suffered 3 severe attacks of acute pancreatitis over 4 years. On each occasion he had abdominal pain and vomiting. A laparotomy was performed during the third attack as the vomiting was so severe that high intestinal obstruction was feared. The pancreas was found to be swollen and inflamed with numerous adhesions between it and adjacent viscera. A scan performed 4 weeks later (Fig.3.24) showed a filling defect in the body of the pancreas. On the strength of this scan appearance re-exploration was advised as it was feared that a carcinoma may have been missed in the inflamed pancreas. A laparotomy 3 months later confirmed the presence of

a necrotic area in the body of the pancreas. This was excised and the pancreas anastomosed to a loop of jejunum. Histological examination of the excised tissue showed only necrotic pancreas with obliterated arterioles but no evidence of cancer. The patient made an uneventful recovery and has remained well for 3 months following the operation.

The cause of the pancreatitis has remained obscure. There was no significant history of alcohol intake, no gall-stones were detected during the most recent laparotomy and the serum calcium was normal.

Chronic Pancreatitis

Patient No.12: A 56 year - old man who was diagnosed as suffering from diabetes mellitus due to chronic pancreatitis in 1962. This was thought to be alcoholic in origin as he professed to a very high spirits intake over the preceding 20 years. In 1967 he had a recurrence of severe abdominal pain following a bout of drinking. Abdominal x-ray at this time revealed calcification of the pancreas (Fig.3.16b). A scan performed 3 weeks after this attack showed a small island of activity in the head of the pancreas alone (Fig.3.16a). At this stage his blood amylase and calcium levels were normal but his fasting blood sugar was elevated (250 mgs./100 ml.) and required insulin injections for control.

Pseudopancreatic Cyst

Patient No.13: A 48 year - old man who was known to have cryptogenic cirrhosis of the liver with portal vein thrombosis and portal hypertension. The patient suffered from recurrent bouts of haematemesis and malaena due to bleeding oesophageal varices. He was submitted to laparotomy in an attempt to perform a spleno - renal shunt. At operation the spleen was mobilized and a splenectomy was performed. The operation was then abandoned because of extensive bleeding. Postoperatively the patient developed a discharging sinus in the left flank which was diagnosed as a pancreatic fistula. Radio - opaque dye injected through a catheter in the sinus was shown to pool behind the stomach (Fig.3.18a). The fistula stopped discharging about 8 weeks postoperatively. Two weeks later he developed an epigastric mass. A barium meal showed an indentation of the greater curve of the stomach (Fig.3.18b) and this approximated to the area of increased uptake on the pancreatic scan (Fig.3.17).

Diabetes Mellitus

Patient No.14: A 67 year - old woman in whom diabetes mellitus was diagnosed 2 years prior to admission and controlled on isophane insulin. Seven months before admission diabetic control became progressively more difficult and the patient suffered frequent hypoglycaemic attacks. These persisted even when the patient was given soluble insulin. Extensive clinical, radiological and biochemical investigation failed to show pancreatic pathology. At laparotomy the pancreas appeared normal and the relationships depicted on the scan were confirmed (Fig.3.9).

Peptic Ulcer

Patient No.15: A 73 year - old man who was submitted to laparotomy because of long standing indigestion and epigastric pain which had become intractable. (Language difficulties made an accurate history impossible). At laparotomy he was found to have a chronic duodenal ulcer in the upper part of the second part of the duodenum. Related to this, and compressing and distorting the neck of the pancreas (Fig.3.20) was a large mass of mesentery and numerous adhesions. The picture was that of a subacute perforation of the duodenal ulcer. The head and body of the pancreas felt normal. A vagotomy and gastro -jejunostomy was performed.

Patient No. 16: A 42 year - old man who had been treated for recurrent bouts of dyspepsia due to duodenal ulcer for 8 years. Two years prior to admission a repeat barium meal showed a gastric ulcer. Five weeks before admission the patient developed an exacerbation of abdominal pain which became more persistant and tended to radiate through to the back. Because he improved very little on intensive conservative therapy over 3 weeks he was submitted to laparotomy. The presence of both a gastric and duodenal ulcer was confirmed. The gastric ulcer, situated on the posterior wall of the stomach was attached to the tail of the pancreas by fibrous tissue. The tail had been pulled upwards and displaced by contraction of the fibrous tissue (Fig.3.19). The signs were those of chronic perforation of a gastric ulcer with involvement of the tail of the pancreas. The pancreas was dissected free and a Billroth I gastrectomy and vagotomy were performed. The patient made an uneventful recovery.

Aortic Aneurysm

Patient No. 17: A 76 year - old woman who presented with a 5 month history of epigastric pain radiating through to the back. Eleven months prior to admission the patient had been treated at another hospital for unexplained iron deficiency anaemia. Besides some epigastric tenderness there were no other clinical signs of note. Barium meal revealed a sliding hiatus hernia but no lesion was seen in the stomach or duodenum. The glucose tolerance test was normal. Pancreatic scan showed a filling defect in the body of the pancreas (Fig.3.21). As her symptoms had not improved after 4 weeks of intensive alkali and anticholinergic treatment the patient underwent laparotomy. At laparotomy the hiatus hernia was repaired. She was found in addition to have a fairly large fusiform aneurysm of the aorta displacing the body of the pancreas anteriorly. The pancreas appeared quite normal on examination.

Patient No. 18: A 66 year - old female with a history of recurrent severe epigastric pain and vomiting for a year. Physical examination was non-contributary. A barium meal showed a large incarcerated hiatus hernia with free reflux in the supine position. At operation the pancreas appeared quite normal but was displaced upwards by a saccular aneurysm of the aorta as depicted on the scan (Fig.3.22).

Fibrocystic Disease of the Pancreas

Patient No.19: (Page 103). A 16 year - old girl who at the age of 5 years started developing recurrent respiratory infections. A diagnosis of bronchiectasis was made at 6 years. After developing steatorrhoea at 7 years the diagnosis of fibrocystic disease of the pancreas was established. Over the next 2 years the patient had several haematemeses and she was noted to have splenomegaly on examination. Liver biopsy revealed cirrhosis and portal hypertension with bleeding from oesophageal varices was diagnosed. The patient continued to have recurrent haematemeses and by the age of 16 years had had several hospital admissions because of this. Her chest also continued to prove troublesome and she had an almost continuous cough with the production of large volumes of purulent sputum. After a particularly severe bout of haematemesis she was admitted for resuscitation and palliative surgery. At laparotomy a spleno - renal anastomosis was performed because the portal vein was found to be thrombosed. Postoperatively a series of recurrent respiratory crises supervened and despite antibiotic therapy, bronchoscopy with bronchial lavage, tracheostomy and oxygen therapy she went progressively downhill and died on the tenth postoperative day.

At post - mortem there were widespread bronchopneumonic changes. The liver showed a mainly macronodular cirrhosis with considerable fatty change. Viscid bile was present in a few ductules. Most of the pancreas was replaced by fat. Ducts were dilated containing mucinous secretion. They were surrounded by fibrous tissue. The islets were relatively well preserved. These autopsy changes were considered to be consistent with the diagnosis of fibrocystic disease of the pancreas.

Primary Amyloidosis

Patient No. 20: (Page 103). A 63 year - old man whose illness began 6 months before his death with sharp, stabbing pains in both legs. Associated symptoms at the onset included anorexia and lassitude. These wore off within a few weeks but the limb pains continued to progress as did the accompanying muscular weakness. The legs were worst affected but the weakness and wasting ascended to involve the trunk and upper limbs. Body dysaesthesia was an outstanding symptom which became progressively worse as the weeks passed. This eventually became so painful and unpleasant that the patient preferred to dry himself after a bath by standing in front of the heater, rather than rub his skin with a towel. There was no family history of nervous diease. On clinical examination the patient when seen 3 months after onset of the illness appeared emaciated and depressed. Examination of the nervous system revealed some loss of power in all limbs, more marked proximally than distally,with greatly diminished tendon jerks. All modalities of sensation were intact as were the cranial nerves. All other systems appeared normal. The blood count was normal as were the blood urea and electrolytes, liver function tests, serum proteins and electrophoretic strip. The glucose tolerance test showed slight impairment with a fasting blood sugar of 94 mgs./100 ml. and a 2 hour level of 110 mgs./100 ml. after a 50 g oral glucose load. Liver biopsy showed a moderately thickened arteriole which stained positively for amyloid with Congo Red. Similar changes were detected in a duodenal biopsy. The patient's condition continued to progress rapidly. In spite of extensive investigation no cause for the amyloidosis could be found and he died 6 months after the onset of the illness. At autopsy there was amyloid infiltration of the heart, liver, adrenals, spleen, pancreas, thyroid, tongue and peripheral nerves. In the pancreas there was extensive vascular and acinar infiltration by amyloid.

APPENDIX 2

Appendix Two

(Prepared with the assistance of Mr. J.E. Agnew, M.Sc..)

Radiation Dosimetry of Se^{75} - Selenocystine

The evidence presented in Chapter 4 shows that, for dosimetry purposes, a dose of 4 μCi/Kg. body weight of Se^{75} - selenocystine may be treated as equivalent to the sum of:

(i) 2 μCi/Kg. of Se^{75} excreted rapidly via the kidneys. For calculation purposes the half-time in the kidneys of this component may be taken as 10 hours - although the experimental evidence suggests that the true figure is probably rather less.

(ii) 2 μCi/Kg. of Se^{75} treated metabolically in the same way as after administration in the form of Se^{75} - selenomethionine.

Radiation Dosage Due to Component (i)

(a) To kidneys

The gamma dose is given by -

$$D\gamma = 0.0346 \rho \Gamma \bar{g} \, Co \, Teff \, r \quad \text{(Ref. 1)}$$

Where the meaning and values of the symbols are as follows:-

ρ = density of tissue (may be taken as 1).

Γ = specific gamma - ray constant - approximately 1.8 /mCi at 1 cm. for Se^{75} (Ref. 2)

$\bar{g}$ = mean geometrical factor - approximately 25 for the kidney (Ref. 3)

Co = initial concentration of Se^{75} in kidney. It may be assumed that about 1 μCi/Kg. goes to each kidney, i.e. 70 μCi per kidney for a standard 70 Kg. man. In a standard man, the kidney has a mass of 300 gm. (Ref. 4)
Thus $Co = \frac{70}{300}$ μ Ci/gm.

Teff = effective half - life = 10 hours.

Using these values, together with a roentgen - to - rad conversion factor of 0.97 (Ref. 5) we get

$D\gamma$ = 3.5 rad.

The beta dose ($D\beta$) is given by

$D\beta = 73.8 \ \overline{E_\beta} \ Co \ Teff$ rads

Where $\overline{E_\beta}$ = mean beta - ray energy per disintegration
0.019 MeV/dis for Se^{75} (Ref. 2)

Thus $D\beta$ = 3.3 rad.

∴ Total dose to kidney from component (i) = 6.8 rad

(b) To pancreas

Difficult to evaluate exactly but certainly much less than from component (ii); i.e. much less that 0.4 rad (see below).

(c) To Liver

Comparatively negligible from this component.

(d) To whole Body

The same formulae are used as in (a) and the same Teff assumed. For a

standard 70 Kg. man $\bar{g}$ may be taken as 126 (Ref. 1). For a 2μCi/Kg. dose Co is 2×10^{-3} μ Ci/gm.

thus $D\gamma$ = 0.15 rad
and $D\beta$ = 0.03 rad

i.e. Total whole - body dose from component (i) = 0.18 rad.

Radiation Dosage Due to Component (ii)

The values below are based on work by Sodee (Ref. 3) - adjusted for a 2μCi/Kg. dose.

a)	To kidneys	8.1 rad
b)	To pancreas	0.4 "
c)	To liver	0.1 "
d)	To whole - body	1.3 "

Radiation Dosage Due to 4μCi/Kg. of Se^{75} - Selenocystine ((i) + (ii))

The dosage due to Se^{75} - selenocystine is shown below, compared ~~conjugated~~ with that due to 3μCi/Kg. of Se^{75} - Selenomethionine.

	4μCi/Kg. Se^{75} - Selenocystine	3μCi/Kg. Se^{75} - Selenomethionine
Kidneys	15.0 rads	12.0 rads
Pancreas	0.8 "	0.6 "
Liver	0.1 "	0.2 "
Whole - body	1.5 "	1.9 "

With Se^{75} - selenocystine, the radiation dosage to the ovary and testes should not be significantly greater than with Se^{75} - selenomethionine.

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APPENDIX 3

The ^{198}Au-Colloidal Gold Liver Scan (Fig.3.).

Rationale:

In the liver the colloidal gold is taken up and retained indefinately by the Kupffer cells (McAfee, Ause and Wagner, 1965). Liver uptake is therefore quite independent of liver cell function. One of the earliest studies on the distribution of intravenously administered ^{198}Au - colloidal gold in man and dogs was performed by Sheppard, Wells, Hahn and Goodell (1947). These authors showed that the distribution of activity was high in liver and spleen, intermediate to low in the kidney and low in other organs. In studying the tumour localization of intravenously administered ^{198}Au-colloid gold in man, Root, Andrews, Kniseley and Tyor (1954) estimated that normal liver tissue probably contained 60 to 94% of the dose, spleen 5 to 16%, kidneys 0.05 to 0.24% and lungs 0.8 to 3.2%. Although there was a large error in estimating the total bone-marrow content it was calculated that it may contain total amounts of the isotope in the same range as the quantities in the spleen. These studies helped establish the fact that there was reticulo-endothelial uptake of the systemically administered ^{198}Au colloidal gold.

This clearance of colloidal gold is very rapid and Christie, MacIntyre, Crespo, and Koch-Weser (1963) have estimated that in normal people less than 10% remains in the blood after 10 minutes. However in patients suffering from advanced cirrhosis with impaired liver blood flow it may take 30 minutes to achieve similar blood levels. An important consequence of the reduced hepatic clearance of colloidal gold in cirrhosis is that the compound is deposited in greater amounts at other sites such as the bone-marrow and spleen.

Dosimetry of ^{198}Au-Colloidal Gold in Man

For practical purposes hepatic clearance of colloidal gold is so efficient that only the radiation dose received by the liver is considered in these calculations. It is estimated by Quimby (1960) that a 2Kg. liver will receive a radiation dose of 5.7 rad from 150 Ci ^{198}Au. Quimby considers that as the average annual dose of 15 rad is applicable, this amounts to about 4 rads per quarter or a permissible injection of 100 Ci of ^{198}Au. She concludes that "the higher dose of 150 Ci may be justified on the basis of medical desirability of the information and the impossibility of obtaining it with smaller doses".

The patients in the ^{75}Se - selenomethionine studies (Chapters 3 & 5) received a standard 110 to 130 Ci dose of ^{198}Au - colloidal gold as this produced a consistently accurate hepatic image.

Technique of Scanning

The ^{198}Au - colloidal gold was supplied by "The Radiochemical Centre", Amersham. The isotope generally required dilution before administration but the volume varied due to the short half-life of ^{198}Au (2.7 days).

The liver scan was commenced 10 to 30 minutes after injection of the isotope and lasted 20 to 25 minutes. The scanner was readjusted to the optimum settings for ^{198}Au (Chapter 2) and the collimator run at 60 cm./minute. To facilitate comparison between the pancreatic and liver scans, the same surface markings were utilized for both.

Results

In keeping with the experience of Whang, Fish and Pollycove (1965) the hepatic scan gave an accurate representation of the true position of the

liver edge as determined clinically.

There was very little discerable splenic uptake unless the liver was diseased. In advanced liver disease, particularly in cirrhosis, splenic uptake was considerably enhanced and marrow uptake (sternum and spine) was sometimes evident. Splenomegaly per se was not associated with ^{198}Au - colloidal gold uptake.

The finding of ^{75}Se - selenomethionine uptake in the area of the spleen as judged by the ^{198}Au - colloidal gold scan was a rare event. When it occurred it was invariably in the presence of splenomegaly and was thought to be a consequence of increased splenic vascularity rather than splenic utilization of ^{75}Se - selenomethionine.

The correspondence between the liver scans with ^{75}Se - selenomethionine and ^{198}Au - colloidal gold was excellent and defects in one were almost always apparent in the other.

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