

Chapter 1: Preoperative Care

1.1 Surgical Nutrition: Enteral and Parenteral

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Introduction

Protein-calorie malnutrition is an important factor that contributes to the increased morbidity and mortality of the hospitalised patient. Several studies demonstrate that between 30 and 50% of patients worldwide have significant depletion of their protein body stores and energy. In addition an acute body mass loss of 30% within 30 days in severely ill surgical patients may prove uniformly fatal. The main aims of nutritional support therefore, are to preserve or replenish body cell mass, and to increase patient tolerance to surgery, radiotherapy and chemotherapy.

Protein Calorie Malnutrition (PCM)

Definition

Malnutrition is a pathological state resulting from a relative or absolute deficiency or excess of one or more essential nutrients. A common definition of PCM is a serum albumin less than 35 g/L, a loss of 10% of usual mass, coupled with an inadequate oral intake of more than two weeks' duration.

Types

- **Undernutrition:** starvation (marasmus)
- **Specific Deficiencies:** electrolyte imbalance, vitamin and trace element deficiencies
- **Overnutrition:** excess calories (obesity)
- **Imbalance:** disproportion of essential nutrients with or without an absolute deficiency (kwashiorkor)

Assessment of Nutritional Status

Aims

- To define the type and severity of malnutrition.
- The identification of high risk surgical patients.
- To monitor response to nutritional support.

Nutritional Parameters

Clinical Appearance

Muscle wasting, angular stomatitis and increased capillary fragility. Subjective global assessment of nutritional status can easily be taught and the technique is reproducible.

Mass Loss

Ten per cent of total body mass, or admission mass less than 30% of that expected for the patient's height.

Anthropometric

Triceps skinfold thickness (TSF) correlates with body fat stores. In the absence of reference values, a value below 10 mm for males and 13 mm for females may be used to indicate need for nutritional support.

- Midarm muscle circumference (MC) is a measure of upper arm muscle mass. It is derived from the formula: $MC \text{ in cm} = 0.314 \times TSF \text{ in mm}$.

- Handgrip dynamometry is a simple test of muscle function. A patient with grip strength 85% (34.0 kg in men, 23.0 in women) is unlikely to develop serious post-operative complications.

Motivation to perform the test maximally is an important factor and normal values are strongly related to age as well as the sex. Other factors which may influence results include body frame, related muscular development and the presence of disease, i.e., arthritis.

Biochemical

Creatinine-height index (CHI) is calculated by expressing the 24 hour creatinine output as a percentage of the mean value, which varies with height. The CHI is more sensitive to changes in nutritional deprivation than mass for height. Values below 80% are abnormal and values under 50% indicate severe muscle wasting. However, as little as a 15 minute error in voiding time for a 24 hour urine collection period leads to a 1% error in estimating creatinine excretion. In addition, excretion over 24 hours is subject to considerable variation.

Serum albumin is not a good index of nutritional status. The half-life of albumin is 18 days. There is also a large albumin pool (4-5 g/kg). Factors besides malnutrition, for example, inflammatory bowel disease and the nephrotic syndrome, may cause a low serum albumin level. However, a rise in serum albumin during total parenteral nutrition indicates a good response to nutritional support and a reduction in post-operative complications.

Plasma transferrin or total iron binding capacity (TIBC): The biological half-life of transferrin is 8 days. The value of transferrin for detecting protein/calorie malnutrition may be limited in the presence of severe iron deficiency anaemia which induces transferrin

synthesis. Transferrin being an acute phase, reactive protein is also responsive to infection and stress. Its concentration may be estimated by the following formula:

$$\text{Transferrin} = (\text{TIBC} \times 0.8) - 43$$

However, each institution using serum transferrin as a nutritional index should either derive its own formula by regression analysis or determine the actual serum transferrin level with radial immunodiffusion kits.

Short-turnover proteins, thyroxine-binding prealbumin (TEPA) and retinol-binding protein have a smaller body pool. The half-life of TEPA is two days. It is responsive to energy intake, and levels may be maintained in protein depletion provided energy intake is maintained. Retinol-binding protein is bound to the TEPA complex. Its biological half-life is 12 hours and it responds quickly to decreased intake of either energy or protein. It is filtered by the glomerulus and metabolized by the kidney; levels are therefore elevated in renal disease.

Plasma fibronectin has recently been included in the nutritional assessment of undernourished patients. It is an opsonic glycoprotein of molecular weight 440,000. Its depletion correlates with reticuloendothelial phagocyte clearance depression. During starvation serum fibronectin values fall by 25-30%.

Immunological Markers

Total lymphocyte counts fall in malnutrition and levels below 1,500/micro are associated with severe malnutrition.

Delayed hypersensitivity skin testing is commonly used but results are conflicting and debatable. Recall antigens used include purified protein derivative, mumps, candida, streptokinase-streptodornase, condition and triachophytin. A positive intradermal skin test is indicated by the development of induration of five millimeters or greater. Patients are classified according to the response to at least five recall antigens as normal (two or more positive), relatively anergic (one positive) or anergic (no positive responses). Anergy has been shown to identify surgical patients at increased risk for sepsis and related mortality. However, skin testing is a poor index of malnutrition because anergy also occurs in the presence of fever, sepsis, malignant tumors, shock, steroid/immunosuppressive therapy and circulating blocking antibodies.

Dynamic Nutritional Assessment

Nitrogen balance: A 24-hour urinary urea excretion, with allowance for extrarenal losses, reflects daily protein requirements in patients receiving parenteral nutrition. Nitrogen supplementation may be based on the formula:

$$\begin{aligned} \text{Nitrogen balance} = \\ (\text{Protein intake } 9 \text{ (g) / } 6.25) - 24 \text{ hour urine nitrogen} \\ + \text{ non-urea nitrogen losses} \end{aligned}$$

24 hour urine urea nitrogen = urine urea mg/L x 24 hour urine vol x 0.028 g. Non-urea nitrogen losses in the absence of diarrhoea average 3 g/day.

3-Methylhistidine (M): m is excreted in the urine. It is considered to represent the turnover and mass of myofibrillar proteins as it is not reutilized. Urinary excretion of m is decreased in patients with protein-calorie malnutrition and in fasting adults. However, studies have suggested that the turnover of M in the intestine is 20 times faster than that seen in skeletal muscle, so even though the intestine may contain only 2% of the whole body pool, it can account for 20% of the excretion under normal circumstances.

Body Composition Studies

Body composition measurements will accurately and quantitatively assess the nutritional state and determine the efficacy of nutritional support. However, the measurements are complex, time consuming and require specialized facilities and trained personnel. They are therefore not suited for the routine clinical laboratory, but are ideal for research purposes. Recently, more sophisticated tests have been developed, i.e. multiple isotope dilution techniques, computerized biostereometrics and plethysmography for body fat, electrical conductivity for lean body mass, CAT scan for skeletal protein, and in-vivo neutron activation for body nitrogen, calcium and phosphorus. Bioimpedance analysis has also gained popularity over the last decade.

Skeletal Muscle Function

The contractile characteristics of the intact abductor pollicis muscle following stimulation of the ulnar nerve have recently been increasingly studied in relation to nutritional rehabilitation in undernourished patients. The maximum force measured at stimulation of 10 Hz and expressed as a percentage of that measured at stimulation of 30 Hz, is significantly increased in malnourished patients. However, the maximal relaxation rate (% force fall/10 ms) is slower in patients. Both variables improve with nutritional support. This improvement is accompanied by restoration of muscle glycogen stores. Muscle function studies are therefore sensitive and specific indicators of malnutrition.

Since many of the parameters used to identify malnutrition are non-specific and imprecise, several different markers of nutritional status have been combined to produce prognostic indexes in an attempt to identify high-risk surgical patients. One such prognostic nutritional index (PNI) is derived from the following formula:

$$\text{PNI \%} = 158 - 16.6 (\text{alb}) - 0.78 (\text{TSF}) - 0.2 (\text{TFN}) - 5.8 (\text{DH})$$

- Alb is serum albumin (g/100 mL)
- TSF is triceps-skinfold (mm)
- TFN is serum transferrin level (mg/100 mL)
- DH is cutaneous delayed hypersensitivity reactivity to any of three recall antigens:
 - 0 = Anergic
 - 1 = Relative anergic
 - 2 = Reactive
- High-risk patients have a PNI > 50%

However, careful clinical assessment, noting cardio-respiratory disease and pre-existing sepsis as well as nutritional state, is as effective as any other currently used indicator of risk.

Energy Balance

The support of protein metabolism is the basic objective of clinical nutritional support; on-going protein synthesis is central to wound healing, immune function and organ structure and function. The supply and utilization of non-protein energy sources are the major determinants of the balance between anabolism and catabolism of amino acids. Utilization of the carbon chain of amino acids as a source of energy results in the excretion of the corresponding nitrogen as urea. Thus the provision and utilization of non-protein energy sources permit the most efficient use of available amino acids for protein synthesis.

Energy Stores and Relationships

All mammals store energy as carbohydrate, fat and protein.

Carbohydrate (CHO)

This is stored as glycogen in liver and muscle. Liver glycogen (75 g) is rapidly metabolized as glucose. Muscle glycogen (200-400 g) is unavailable to support blood glucose except by the release of lactate and pyruvate and subsequent transfer of these to the liver for gluconeogenesis (Cori cycle). One gram of carbohydrate yields 4 kCal (16.8 kJ) and approximately 1500 kCal (6.3 MJ) are stored as carbohydrate in the body. Glucose is the CHO of choice, being the normal physiological substrate and essential for cerebral metabolism. The minimum amount of CHO necessary for neural and red blood cells is 100-150 gm daily. In normal subjects, glucose is oxidized at 2-4 mg/kg/min (approximately 250 mL/hr of 5% dextrose in a 70 kg man). This rate is unaltered by hyperinsulinaemia or hyperglycaemia. When glucose intake exceeds the maximal oxidative rate, the excess is converted to fat, while a caloric deficit persists.

Stressed patients exhibit a maximal glucose oxidation rate of 3-5 mg/kg/min. Hyperglycaemia is also more common under these conditions. During overfeeding, conversion of CHO to fat raises the RQ further ($RQ = .87$) the resultant excessive production causes a compensatory rise in minute ventilation.

Fructose can be substituted for glucose provided the infusion rate does not exceed 0.5 g/kg/h. However, the danger of lacticacidosis in the very young, shocked patients and in liver failure must be borne in mind. Hyperuricaemia and a decrease in adenine nucleotide and inorganic phosphate are added disadvantages. Invert sugar, sorbitol and xylitol have no practical advantage over dextrose, the latter two being associated with metabolic acidosis.

Ethanol (96%) provides 7.1 kCal/g (29.4 kJ/g). The intake should not exceed 1.5 g/kg/day. Fructose and ethanol combinations increase the risk of lacticacidosis. Acute folate deficiency may also be a problem.

Fat

This is stored as triglyceride. One gram fat yields 9 kCal (37.9 kJ) and approximately 90,000 kCal (378 MJ) are stored as fat. The minimum dietary fat requirement is that which will prevent essential fatty (linoleic) acid deficiency (EFAD). This is manifested by a dry skin rash, ecchymoses, alopecia, anaemia, oedema, thrombocytopaenia, and respiratory distress. A triene:tetraene ratio greater than 0.4 is diagnostic. Patients with glucose intolerance (except hyperlipidaemic diabetics) may tolerate fat calories better than carbohydrate. Fat does not interfere with dialysis, but azotaemic patients are frequently hyperlipidaemic, which may impair their fat tolerance.

The side-effects of intravenous fat emulsions increase with high doses. While pyrogenic reactions occur in 3% of patients, up to 3 g/kg/day of lipid produces no major side-effects. Fat administration in excess of 3 g/kg/day in infants and 4 g/kg/day in adults produces a fat overload syndrome consisting of hyperlipidaemia, coagulopathy, fever, cholestatic jaundice and gastro-intestinal distress. Lipid microaggregates in the liver produce cholestasis and in the lung, impair diffusion and may produce an adult respiratory distress syndrome.

Medium-chain triglycerides (MCT) are a suitable carnitine-independent energy source for total parenteral nutrition. They should not be used solely as fat calories, but as supplementary energy to long-chain fatty acids, which must also provide essential fatty acids. As little as 500 mL of a 10% lipid emulsion, administered twice weekly, will prevent essential fatty acid deficiency.

Protein

One gram of protein yields 4 kcal (16.8 kJ). However, all body protein is considered to be functional and mobilization of protein to meet energy demands is detrimental. Increasing protein intake improves nitrogen balance only when energy supply is adequate. A desirable calorie to nitrogen ratio is generally between 135:1 to 200:1 (kcal:gm nitrogen). A non-stressed patient needs 250 mg nitrogen/kg/day, while stressed patient may need up to 400 mg/kg/day. Special properties of the branched chain amino acid (BCAA) which include valine, leucine and isoleucine, have recently been emphasized. They are an important energy source for muscle, being oxidized directly within the muscle without glucose as an intermediary. In sepsis, with glucose resistance, increased amounts of the branched amino acids may be more appropriate for the injured organism. Furthermore, the BCAAs play a role in the regulation of protein synthesis, suggesting beneficial effects in catabolic states such as post-operative stress, trauma, renal failure and burns. However, initial studies in these areas have presented equivocal results. It should be emphasized that BCAAs are administered as a mixture of essential and non-essential amino acids enriched up to 50% with BCAAs.

Energy Requirements

It had long been thought that patients needed 4000-5000 kcal/day (16.8-21 MJ) to maintain a positive caloric balance. It has now been shown that 200 kcal/day (8.4 MJ) will suffice for the majority of patients. Accurate measurements of total energy expenditure are difficult to obtain in the clinical setting. Malnourished patients without sepsis, whether pre- or post-operatively, have a low metabolic rate (up to 20% below predicted). Malnourished

patients developing major post-operative sepsis have a metabolic rate of up to 25% above the predicted. If sufficient protein is given, protein retention can occur even if estimates of total energy expenditure are off by 20-30%.

Methods for Calculating Resting Energy Expenditure

- Harris-Benedict equation with appropriate adjustments made for the degree of stress and activity.

- Indirect calorimetry, i.e. measuring CO₂ production and O₂ consumption using a metabolic computer.

Goals of Nutritional Support

- To maintain or replenish the body cell mass.
- To decrease patient morbidity and mortality.

Indications for Nutritional Support

- Normal gastro-intestinal tract with normal access - multiple trauma, burns, severe sepsis, cancer, renal and hepatic failure, anorexia.

- Normal gastro-intestinal tract with impaired access - patients with oesophageal cancer, peptic stricture or pyloric stenosis.

- Abnormal gastro-intestinal tract - Crohn's disease, ulcerative colitis, tuberculous enteritis, short bowel syndrome, radiation enteritis.

- Paediatric conditions i.e. congenital malformations of the gastro-intestinal tract (oesophageal and intestinal atresias, gastroschisis), necrotizing enterocolitis.

Before initiating nutritional support the patient must be haemodynamically stable, adequately oxygenated and in normal acid-base and electrolyte balance.

Choice of Method of Nutritional Support

Both the oral and intravenous routes may be used for nutritional support. The two methods should be considered as complementary. Oral alimentation should always be considered first, provided that the gastro-intestinal tract is intact and functional.

Enteral Alimentation

This is the most physiological and effective way of providing nutrients. It is safe, simple and economic. Absolute contraindications to enteral feeding include intractable vomiting, intestinal obstruction and profuse gastro-intestinal bleeding.

A variety of internal feeding mixtures is available, so that an appropriate choice can be made to satisfy any given patient's specialized needs (table 1.1.1). Polymeric formulas may be food-based or contain combinations of intact macronutrients. Blenderized food tube feedings are commercially or individually prepared. They are nutritionally complete, cause few gastro-intestinal side effects if delivered into the stomach, promote normal gut function, and are inexpensive. Chemically defined formulas contain monomeric or short-chain hydrolysis products of protein and carbohydrate macronutrients. They are lactose free. However, calorie needs may not be met efficiently with the predominantly carbohydrate calories source, especially in stressed patients. Special formulas have been designed to nourish patients with liver or renal diseases. A branch-chain amino acid enriched formula with medium chain triglycerides and low electrolytes attempts to improve the metabolic abnormalities of liver failure.

Modular products provide one or a few macronutrients only, and no micronutrients. They cannot provide complete nutrition.

Initially the patient should be allowed to drink the solution, usually a volume of 2 L divided into three to six portions. If this is unsuccessful, tube-feeding should be attempted. The oropharyngeal irritation, upper airway hypersecretion and oesophageal reflux associated with larger, more rigid tubes are minimized with small-bore flexible tubes. Pulmonary aspiration is less likely when the catheter tip negotiates the pylorus. The patient's head should be elevated during and after feeding. Diarrhoea is the most common gastrointestinal side effect of tube feeding. It may result from excess volume, hyperosmolarity of the diet and malabsorption due to functional atrophy of the intestine. Diarrhoea usually responds to lowering the infusion rate and reducing the osmolarity of the solution. In a recent double-blind controlled trial in patients with normal gastro-intestinal function who were fed a polymeric diet by constant nasogastric infusion, starter regimens reduced nutrient intake but not the incidence of diarrhoea or other gastro-intestinal side-effects. Undiluted hypertonic polymeric diets infused from the onset of feeding resulted in significantly better nitrogen intake and balance. Diarrhoea, when present, was related to antibiotic usage. A newly designed polyurethane nasogastric feeding tube has been shown to have advantages over the simpler type of open-ended, unweighed polyvinylchloride nasogastric feeding tubes.

Parenteral Nutrition

Total parenteral nutrition (TPN) is a technique of providing all nutrients entirely intravenously. Vascular access may be via either central or peripheral veins.

Central TPN

Central venous access is usually achieved via the subclavian or internal jugular veins. Insertion of a central venous catheter for TPN can be a safe and effective procedure with minimal risk of complications. It is important that a precise protocol be followed on all occasions by the team involved. Strict aseptic technique must be maintained. A 35 cm silicone catheter with detachable hub (Vygon) is frequently used for TPN. More recently, double and triple lumen catheters have also been evaluated as nutrition catheters. A chest X-ray must be done to check catheter position and to exclude complications of insertion before any

hypertonic solution is given. The infusion should therefore begin with an isotonic solution such as Plasmalyte L.

Dressing Procedure

The administration set and occlusive dressings are replaced every third day. The skin must be cleaned mechanically using acetone and povidone-iodine. Iodine ointment or spray should be applied to the exit site at each change. Skin swabs are cultured weekly. The central line should not be used for central venous pressure monitoring, administering blood or taking blood samples for routine laboratory investigations. The administration of antibiotics through the central line is also avoided. If necessary, they should be given through an independent peripheral venous line or a double lumen catheter may be used. Inappropriately placed cannulae are redirected into the superior vena cava using sterile stainless steel guide wires under fluoroscopic control, prior to administration of hypertonic dextrose. This technique is also valuable when recatheterization is necessary.

Catheter-related sepsis in the majority of patients is the result of poor local catheter care. Organisms invade the catheter from the skin. The following logic flow chart is essential to control and exclude catheter sepsis:

- Clinical examination
- RBC, WCC and blood culture (peripheral)
- Swab from catheter entry site
- Culture urine, sputum
- Appropriate X-rays, ultrasound, CAT scan.

If there is an obvious source of infection (wound infection, pneumonia, urinary tract infection, intra-abdominal abscess), it should be treated and TPN continued. If there is no clear source of infection, the administration set and infusate should be changed.

If fever persists after 24 hours of broad-spectrum antibiotic cover, the central venous catheter should be removed and the tip cultured for bacteria and fungi. The catheter should be removed from any patient with a positive blood culture. Parenteral nutrition should then be continued via a peripheral vein. The nutritional catheter must be regarded by all in attendance as the patient's life-line. On removal of the catheter the exit site must be covered with a sterile gauze dressing to prevent air embolism.

Mixing Considerations

Intralipid 10% and 20% (fat emulsion), amino acids 10% and dextrose (50% solution) may be combined to form a three-in-one solution. This is easier to administer, reduces the need for nursing supervision and reduces the risk of infection inherent in "piggy-backing" lipid emulsions. Mixing is carried out in the pharmacy under sterile conditions within a laminar flow hood. Lipid should be mixed with the amino acid solution before mixing with

acidic dextrose solutions, cations, and other additives. Whenever lipid is used, bags made of ethylene vinyl acetate should be used instead of polyvinyl chloride containers to prevent lipid container interaction. Electrolytes, vitamins and trace elements can safely be added to the TPN solution in reasonable therapeutic quantities. Heparin, cimetidine, hydrocortisone, albumin, iron, dextran, aminophylline and insulin are also compatible with the all-in-one system.

Peripheral Intravenous Nutrition

By using fat emulsions to provide 30 to 60% of caloric intake, full energy and protein requirements can be provided via a peripheral vein. Solutions with an osmolality greater than 600 mmol/L or with potassium concentrations greater than 60 mmol/L are more likely to cause phlebitis. This risk may be minimized by adding 1000 units of heparin and 5 mg of hydrocortisone to each litre of solution. In a study of 15 patients with oesophageal cancer, peripheral vein alimentation using the dual energy system proved an effective method of preventing progressive nutritional depletion. The infusion technique was safe and was without serious metabolic or infectious complications.

Cyclic TPN

This provides nutrient infusion over 12 to 16 hours per day. During the non-infusion period, a low insulin state allows mobilization of endogenous fat. This technique decreases hepatic lipogenesis and improves hepatic function. It allows the patient more mobility and is the usual mode of administration in patients on home TPN.

Total parenteral nutrition regimens should be gradually increased in order to assess patient tolerance to hypertonic solutions and to allow for the metabolic adaptation to the fed state. It should continue until normal gut function returns. Enteral feeding should be introduced in increasing concentrations, synchronously reducing parenteral infusions, until the total requirement can be given enterally.

Monitoring the Patient

- Clinical examination daily and note response to TPN
- Fluid, electrolyte and nutrient requirements determined daily
- Baseline nutritional assessment and thereafter weekly
- Biochemistry - U/E, blood sugar, Hb, calcium and phosphates, LFT, Pi, Mg, Fe and TIBC, Zn, Cu, and acid base studies weekly
- Blood culture, catheter site cultures once per week
- Base-line nitrogen balance studies and thereafter weekly once the patient is stable
- "Pull-out" phlebogram and catheter-tip culture on termination of TPN
- Ultrasound of gall bladder on admission and then fortnightly.

Complications of TPN

Catheter Related

- Mechanical - central vein thrombosis, catheter embolization, haemopericardium and tamponade, arrhythmias, haemo/pneumothorax, air embolism, tracheal puncture, arterial laceration and brachial plexus injury.
- Sepsis - the acceptable sepsis rate is 3%. Staphylococcus epidermidis and candida albicans are infecting agents during TPN.
- Blocked catheter - this is due to stagnation of fluid within the intravenous line when the delivery system is inadvertently clamped off or allowed to run dry. The incorporation of an infusion pump may decrease this complication. The addition of heparin in concentrations of 2000 units/L of infusate has been shown to prolong catheter life by decreasing thrombotic occlusion and embolism. However, in other studies, heparin failed to confer protection against thrombosis. Catheters composed of silicone, polyurethane and Teflon are the least likely to be associated with major thrombi.

Metabolic

- Hyperglycaemia - this is the commonest and most important metabolic complication. The addition of soluble insulin to the nutrient infusion is the most effective method of control (1 unit of soluble insulin for every 10 g dextrose). Control is also facilitated if a constant glucose concentration and pump infusion rate are used. Blood glucose concentrations should be kept below 14 mmol/L. Rebound hypoglycaemia can be prevented by ensuring a constant glucose infusion.
- Electrolyte and acid base abnormalities - i.e. low-serum K⁺, Mg⁺⁺, Ca⁺⁺, phosphate, Na⁺ and metabolic acidosis. Hyperchloraemic metabolic acidosis may occur with the liberation of hydrochloric acid during amino acid metabolism. It can be prevented by the routine addition of 15 to 30 mmol of acetate to each litre of parenteral solution. Thiamine deficiency may predispose to lactic acidosis.
- Essential fatty acid deficiency may occur after two weeks of fat-free parenteral nutrition.
- Vitamin deficiency, i.e. thiamine, especially in alcoholic patients.
- Trace element deficiency - especially zinc.
- Bone disease - long-term TPN may cause overt rickets and osteomalacia.

Hepatic Function Changes

- There is a transient rise in alkaline phosphatase, bilirubin and transaminases. These changes are associated with both enteral and parenteral feeding. An important underlying cause which must be excluded is intra-abdominal sepsis.

- Cholestasis and biliary sludge may be related to decreased cholecystinin production consequent to reduced intraluminal and chemical stimulation. TPN is also associated with acalculous cholecystitis which is associated with increased morbidity and mortality especially in the paediatric patient.

Gastro-Intestinal Tract Changes

TPN is associated with hypoplasia and atrophy of intestinal mucosa. The supply of oral nutrients prevents this complication.

Home Parenteral Nutrition

Patients with short bowel syndrome, extensive Crohn's disease and other irreversible causes of malabsorption can now be maintained on home parenteral nutrition. The aim is to infuse nutrients intravenously during a 10 to 12 hour overnight period to approximate daily requirements while encouraging the patients to pursue normal activities during the day. Careful evaluation of the patient's physiological state and social background must be undertaken before embarking on home therapy. The patient's family must also be actively involved in the rehabilitation programme. A patient must be medically stable for home TPN. It should not be undertaken when the risks of home TPN are judged to exceed the potential benefits.

The Team Approach

It is essential to provide a TPN service with minimal complications and a high degree of effectiveness. Several studies have conclusively demonstrated that an organized nutritional team provides better patient care. Included in the team are a surgeon and a physician, a pharmacist, an alimentation nurse, a dietician, microbiologist, physiotherapist, stomatherapist and a social worker. The team approach also improves clinical competence among junior staff and stimulates research projects. Although there is enough favourable evidence in cost-effectiveness for a hospital nutrition support team, the full potential of such a team has yet to be widely recognized and properly tested.

Cost-Effectiveness of TPN

To keep TPN cost effective, it should be used only when indicated, only in patients where a clear-cut benefit has been demonstrated and when complications can be kept at an acceptable level.

Nutritional Support in Clinically Relevant Situations

Pre- and Post-Operative Nutritional Support

Supplementary intravenous feeding should be given to malnourished patients, particularly those with cancer of the upper gastro-intestinal tract, before surgery is undertaken. In this group of patients malignant cachexia and immunoparesis increase the postoperative morbidity and mortality. Improvement in the nutritional status of cancer patients by oral feeding may be difficult because of anorexia, mechanical obstruction and malabsorption, or

it may take so long that adequate antineoplastic therapy is delayed. Total parenteral nutrition is then necessary.

The objectives of nutritional repletion are enhanced wound healing, a reduction in post-operative complications and more rapid convalescence. In non-depleted postoperative patients who are unable to eat or absorb food adequately one week after the operation, parenteral nutrition providing 0.8-1 g of amino acids per kilogram of body mass per day and a total number of kilojoules 20% above the basal energy expenditure should be instituted. In depleted patients this increases to 1.5-1.8 g/kg amino acids and a total kilojoule intake 50% above estimated basal energy expenditure. Postoperative parenteral feeding with amino acid and hypertonic glucose solutions is more effective in preventing postoperative catabolism, promoting tissue protein synthesis and reducing complication rates than infusion of 5% dextrose with electrolytes.

High-Output Fistulas of the Alimentary Tract

The treatment of gastro-intestinal fistulas has been associated with significant morbidity and mortality rates as high as 65%. The prognostic importance of nutritional status in the management of fistulas was first emphasized by Chapman et al who dramatically reduced mortality by correcting malnutrition before the surgical closure of fistulas. More recently, Voitk et al using a chemically formulated diet, reported a mortality rate of 28% and MacFayden et al by treating gastro-intestinal fistulas with total parenteral nutrition achieved a mortality rate of 6.4%. Treatment without nutritional support will result in a high mortality rate, particularly in association with early, aggressive surgery. Moreover, if the patient survives, recurrence of the fistula is common. Definitive surgical closure of the fistula should be performed only when the patient is afebrile and has good nutritional status, and if the fistula effluent shows no sign of decreasing in volume after six weeks of nutritional support. Most postoperative fistulas can be prevented. Of particular importance is the avoidance of enterotomy as a method of decompressing obstructed bowel, and careful suture repair of the extensive serosal tears which may follow the lysis of adhesions.

Pre-operative nutritional repletion will also help to decrease the incidence of postoperative fistulas. Our experience in the management of 63 patients with high-output alimentary tract fistulas treated over a three-year period, using three different regimens of nutritional support, showed a spontaneous closure rate of 73%, while another 11% were cured by direct surgical closure. The combination of nutritional support, skin protection and timed surgical intervention can reduce the mortality rate in this group of patients to below 10%. Sepsis must be treated aggressively as this is the major factor in mortality and morbidity.

Cancer

Cachexia is the commonest cause of death in cancer patients. The reduction in body cell protein leads to respiratory inefficiency and terminal respiratory infection. Cancer cachexia is a multifactorial entity and is clearly affected by anorexia, gastro-intestinal malfunction and abnormalities of taste. Tumour metabolism, necrosis and infection together with surgery, radiotherapy and chemotherapy, can all contribute, singly or in combination, to the mass loss that often attends treatment. Protein-calorie malnutrition also contributes significantly to the immunoparesis evident in patients with cancer, and this may be an

important factor in tumour prognosis, immunotherapy and the immunoparesis of solid tumours.

The main aims of nutritional support in the cancer patient are to maintain or replenish body cell mass and to increase patient tolerance to surgery, radiotherapy and chemotherapy. With recent advances in nutritional support, the metabolic effects of tumour metabolism can be reversed by parenteral or enteral feeding. Reports on the treatment of malnourished cancer patients with total parenteral nutrition during the period of antineoplastic therapy indicated a reduction in morbidity and mortality. Yet other prospective studies failed to show a beneficial effect of total parenteral nutrition as an adjunct to surgery, chemotherapy and radiotherapy. Characteristic of these reports is a response advantage for non-randomized patients who were malnourished and no-response advantage in the randomized trials for patients not malnourished.

Skeletal muscle function has recently been increasingly studied in relation to nutritional rehabilitation in undernourished patients. The force-frequency characteristics and maximal relaxation rate of the adductor pollicis muscle improved significantly after glucose-potassium loading. This improvement was accompanied by restoration of muscle glycogen levels and return of respiratory exchange ratios towards unity. These results imply that if muscle power can be regarded as a yardstick of preoperative nutritional rehabilitation, then a simple regimen of energy-electrolyte repletion may be cost-effective in preparing malnourished patients for major surgery.

A worrying aspect of nutritional repletion of the cancer patient is whether feeding would accelerate tumour growth. Short intervals of nutritional repletion have not been associated with accelerated tumour growth in human cancers. Clinically there is also no increase in septic complications and catheter related sepsis remains less than 3%. Cell cycle kinetics using flow cytometry in patients with untreated squamous carcinoma reveal that the percentage of hyperploid cells, aneuploidy and the S and G2M phases of the cell cycle are significantly increased after three to 17 days of total parenteral nutrition. Intravenous feeding, therefore, will stimulate tumour growth to some extent. This suggests that the sensitivity of cancer cells to some forms of cycle specific chemotherapy may be altered by nutritional repletion.

The role of nutritional support as an adjunct to cancer therapy remains undefined. It can only transiently reverse or alleviate the depleted state and cannot palliate or eradicate the underlying malignancy. More data are needed to determine the particular requirements of the cancer-bearing host as well as the tumour. In addition, optimal total parenteral nutrition mixtures and various nutritional metabolic therapeutic interventions need further evaluation. In the interim, non specific nutritional support may serve as an essential adjunct to cancer therapy in malnourished cancer patients who receive aggressive and effective antineoplastic therapy. Patients most likely to benefit from nutritional support include hypoalbuminaemic patients awaiting major surgery. However, few patients will require more than 8.3 Mj/day (2.000 kCal/day). In the absence of specific cancer therapy, routine nutritional support of the cancer patient seems unjustified.

Short-Bowel Syndrome

Extensive intestinal resection for inflammatory bowel disease or mesenteric vascular occlusion can result in the development of short-bowel syndrome. Adequate nutritional support is essential for the survival and rehabilitation of these patients. Total parenteral nutrition should be maintained for approximately 21 days in order to allow compensatory adaptation in the residual healthy intestine. During the postoperative period chemically formulated diets have a distinct advantage over normal foods. These diets are almost totally absorbed in the upper small intestine with minimal digestive requirements. A high-carbohydrate, high-protein, low-fat diet should be the final goal in nutritional therapy. Intestinal absorption is also more complete with frequent feedings of equally divided portions of nutrients. Gastric hypersecretion may complicate the short-bowel syndrome but this is usually an acute and temporary phenomenon. Ambulatory home care using total parenteral nutrition is a novel and optimistic approach for patients with inadequate residual bowel; these patients are now able to live under conditions of almost total social rehabilitation.

Inflammatory Bowel Disease (IBD)

The activity of IBD can be reduced by bowel rest, especially when the site of involvement is the small intestine. Nutritional support in patients with small-bowel Crohn's disease will increase total plasma proteins, reduce protein loss into the gastro-intestinal tract and increase peripheral blood lymphocyte counts.

It is generally conceded that the role of parenteral nutrition in the treatment of patients with IBD is adjunctive to surgical or medical management. The best results are found in those patients with regional enteritis confined to the small bowel - a remission rate of 75% has been reported. Less favourable results in patients with active, non-fistulous Crohn's disease treated with parenteral nutrition have been reported in prospective trials. Steroid dosage may be reduced to 5-10 mg/day in patients receiving nutritional support. Granulomatous disease involving the colon is associated with a lower remission rate, and regardless of the severity of disease, the response to parenteral nutrition in patients with ulcerative colitis is poorer than in those with Crohn's disease. Entero-cutaneous fistulas complicating Crohn's disease may heal but frequently reopen once oral feeding is resumed. Resection is indicated in such circumstances. Patients with IBD are more prone to complications during total parenteral nutrition. They also tend to develop antithrombin-III deficiency and may be more prone to subclavian vein thrombosis.

Burns

Major thermal injury is characterized by a hypermetabolic response, the magnitude of which parallels the extent of the thermal injury and may be 150-200% of the normal resting metabolic expenditure. Such hypermetabolism is associated with markedly increased energy requirements. Indeed, mass loss may not be totally prevented even when an intake of 37-42 Mj/day is achieved by combined enteral and parenteral feeding. Patients with major burns treated with aggressive nutritional support have a higher survival rate, but catheter-related sepsis tends to be more common in this group. Since in severely burned patients sites of access may be limited, central catheters are used for the administration of all fluids as well as for parenteral nutrition, but are changed more frequently.

Nutritional Support of Patients with Major Burns Include:

- control of external environment - maximum comfort is afforded at 30 °C
- prevention of septic complications
- early wound debridement and skin closure
- physiotherapy and early ambulation
- provision of adequate exogenous calories - 40 kCal/kg/day + 40 kCal% burn/day and 1.4 g protein/kg/day.

Severe Trauma or Infection

Severely traumatized, ventilator-dependent patients have increased metabolic demands (20-60% above basal requirements). Together with this, multiple organ failure and sepsis lead to the rapid development of protein-calorie malnutrition. A review of the nutritional status of patients supported by ventilation showed an almost universal iatrogenic malnourished state. This group of patients should be considered for nutritional support after an initial 48-hour period which allows for adequate resuscitation, oxygenation, correction of fluid, electrolyte and acid-base imbalance, initiation of appropriate antibiotics and surgery. Where glucose is the sole energy source, the respiratory quotient is increased as a result of increased carbon dioxide output. Metabolic acidosis develops and this may further compromise pulmonary function in severely ill patients. In septic states there is modulation of the action of pyruvate dehydrogenase leading to blockade of the entry of pyruvate into the citric acid cycle, with resultant decrease in oxidation of glucose and insulin resistance.

There is a system for classifying stressed surgical patients based upon patterns of nitrogen excretion, urinary 3-methylhistidine excretion, plasma lactate levels, and blood glucose levels. Such a system is useful in identifying seriously catabolic patients and to guide nutritional efforts more rationally.

Branch-chain amino acids, leucine, isoleucine, and valine serve as a preferred oxidative substrate in peripheral skeletal muscle and may stimulate muscle and visceral protein synthesis. However, its use in the severely ill patient remains undefined.

Miscellaneous Conditions

Liver Failure

Nutritional requirements are different in patients with liver failure, particularly as regards protein and vitamins. Protein intolerance is a consequence of both increased endogenous protein catabolism and reduced amino acid clearance by the liver. Consequently, diets low in aromatic amino acids and high in glucose are commonly advocated. More recently branch-chain amino acid supplements (BCAAs) have been added, for the reason that tolerance is normal because they are oxidized extrahepatically.

Given at a constant rate of 3 g/hour amino acids are within tolerance levels. Patients also require increased supplements of water and fat-soluble vitamins.

The exact rate of fat emulsions in liver disease is not defined. Theoretically, fatty acids may increase the risk of encephalopathy by displacing the albumin-bound tryptophan but it has also been shown that fat degradation in patients with liver disease is increased from 50-84% of the normal value. Fat therefore appears to be an important substrate in severe liver disease.

Renal Failure

Whether nutritional support alters overall survival and hastens recovery of renal function in patients with acute renal failure, has not been elucidated. Once the need for dialysis is established, most clinicians use a combination of essential and non-essential amino acids, because both types of amino acids are lost during dialysis. The nitrogen lost with dialysis ranges from 2 g/haemodialysis to 9 g in a peritoneal dialysis. The effects of the increased nitrogen load can be ameliorated by dialysis. However, the precise role of essential amino acids alone versus mixtures of essential and non-essential amino acids in treating patients with acute renal failure remains controversial. Histidine and perhaps arginine may be regarded as being essential in adults with renal failure. The use of hypertonic glucose as an energy source is associated with a lower incidence of uraemic encephalopathy. Particular attention should also be paid to fluid, potassium, magnesium and phosphate needs in this groups of patients.

Cardiac Failure

Malnutrition can lead to cardiac dysfunction and, conversely, cardiac impairment can lead to malnutrition, commonly referred to as cardiac cachexia. Sudden death due to ventricular fibrillation has been documented in otherwise healthy individuals consuming inadequate amounts of protein. Intracellular electrolyte and trace element deficiency not detected by routine clinical testing may have contributed to the arrhythmia.

Pancreatitis

Total parenteral nutrition may be used in patient with severe pancreatitis (regardless of aetiology) with minimal technical or metabolic morbidity, and has contributed in part to a reduction in overall mortality. Approximately 10% of patients will require parenteral nutritional support. Initial glucose intolerance is common but is easily controlled by decreasing the infusion rate or by the addition of soluble insulin (20-30 u) to the parenteral mixture.

Patients must be carefully monitored for elevations of serum calcium and amylase levels during total parenteral nutrition. Parenteral nutrition in pancreatitis fulfills a supportive role, but when patients are referred for laparotomy, jejunostomy should be performed as a means of long-term nutritional support.

Principles in Planning Total Parenteral Nutrition

- Energy intake 40-50 kcal/kg (adult) 70:30 basis CHO:Fat
- Nitrogen 0.2-0.3 g/kg
- Optimum ratio of K⁺:nitrogen of 5-6 mmol; NMg⁺⁺ as 1-1.5 mmol g N
- 0.3 mmol phosphorus/kg
- Fat 2-3 g/kg. Never provide more than 70% of the calories
- Nitrogen and an energy source must be given simultaneously
- Symptomatic hypoalbuminaemia corrected by albumin or plasma infusions
- Patient must be mobilized early
- After two weeks, consider essential biological trace elements
- Reassess nutritional requirements daily
- Calorie:Nitrogen ratio of 150-200:1
- Occupational therapy

Comment

Surgical Nutrition: Enteral and Parenteral

W L Michell

The provision of adequate nutrition is an essential part of intensive therapy support for the critically ill patient. Wherever possible the enteral route should be used, but frequently recent surgery and gastrointestinal dysfunction associated with critical illness makes intravenous nutrition essential. Septic patients pose a particular problem and will continue to have a net nitrogen loss even when provided with adequate calories and amino acids. *The severe muscle proteolysis that occurs in septic, critically ill patients provides an endogenous source of amino acids for the hepatic synthesis of proteins and wound healing.* This catabolic state, which leads to profound muscle weakness and can delay weaning from the ventilator, is in part controlled by cytokines produced by macrophages and other reticuloendothelial cells. Tumour necrosis factor (TNF) and proteolysis inducing factor, a cleavage product of interleukin-1 appear to be important in mediating this catabolic process.

Nutritional assessment of critically ill patients is notoriously difficult. Body mass and skinfold thickness are affected by fluid sequestration and haemodilution lowers plasma proteins. New microprocessor-based metabolic monitors are now available for continuous, on-line, indirect calorimetry in ventilated patients.

Enteral feeding may be introduced via a soft, silastic nasogastric or nasoduodenal tube or by means of a surgically placed feeding jejunostomy or percutaneous gastrostomy. Enteral feeding carries a risk of tube displacement, regurgitation and pulmonary aspiration. Slow continuous feeding using a flow rate controller with the patient in an upright position, minimizes regurgitation.

If enteral feeding is not possible, a central line is required as access to peripheral veins is often limited. In addition, critically ill patients frequently have to be volume restricted and the most concentrated intravenous solutions available may be required.

Catheter sepsis is a frequent problem in the ICU as it is seldom possible to limit the central line to nutritional use only and catheters can become infected by endogenous bacteraemias. Catheters should be changed regularly as the incidence of catheter sepsis increases after 72 hours of catheter placement.

Critically ill patients require increased quantities of amino acids - 1.5 to 3 g/kg/24 hrs, but caution should be exercised if there is evidence of renal or hepatic failure. Most critically ill patients have measured metabolic rates in the region of 1.1 to 1.4 times the calculated basal energy expenditure. Glucose as the sole source of energy is not satisfactory as there is a high incidence of hyperglycaemia which is difficult to control with insulin. Thirty to 50% of the energy source should be supplied as lipid.

Although the benefits of intravenous nutrition in critically ill patients are difficult to demonstrate in clinical trials, undoubtedly survival of a prolonged critical illness is dependent on adequate nutritional support. Intravenous nutrition in these circumstances is fraught with complications, and this can only be reduced by meticulous attention to detail and continuous surveillance.

1.2 Fluid and Electrolyte Therapy

A A Haffejee

Aims of Fluid and Electrolyte Therapy

- Maintenance of cardio-vascular homeostasis, i.e., blood volume, cardiac output, oxygen transport
- Maintenance of effective renal function
- Maintenance of normal body fluids and electrolytes within the extra and intracellular compartments

Anatomy and Physiology of Body Fluids

In a normal, 70 kg adult male, total body water (TBW) makes up approximately 60% of body mass. This TBW is influenced by age, sex and lean body mass, but in health it remains remarkably constant from day to day. Adipose tissue contains little water; therefore obese individuals may have up to 25-30% less water than lean individuals of similar mass. For the same reason, the average female has less body water than the average male. TBW is divided into intracellular (ICF) and extracellular (ECF) compartments. ICF represents about two-thirds of TBW, or 40% of body mass. The remaining one-third of body water is ECF. ECF is divided into two compartments:

- Plasma water, comprising approximately 25% of ECF, or 5% of body mass
- Interstitial fluid (ISF) comprising 75% of ECF, or 15% of body mass.

Unlike plasma which is located intravascularly, interstitial fluid is the fluid which surrounds tissue cells and is located outside the vasculature. Lymph, CSF, peritoneal, pleural, synovial and pericardial fluids are also considered to be ISF. The ISF and plasma communicate with one another across the capillary wall. The cell membrane separates the intracellular and extracellular compartments. The osmotic flow of water across the cell membrane governs the distribution of body water between the ICF and ECF compartments.

Electrolyte Count

The various ions are similar in plasma and ISF but vary intracellularly from tissue to tissue:

- ICF has a higher concentration of K, Mg and the main anions are phosphate and protein

- Plasma has a higher concentration of Na with low K, Mg and the main anions are chloride and bicarbonate

- ISF is almost the same as plasma with more Cl and less protein. The plasma proteins, chiefly albumin, account for the high colloid osmotic pressure of plasma which is an important determinant of the distribution of fluid between vascular and interstitial compartments, as defined by Starling relationships.

The kidneys maintain the volume and composition of body fluids by two distinct but related mechanisms:

- filtration and reabsorption of sodium

- regulation of water excretion in response to antidiuretic hormone

These two mechanisms allow the kidneys to maintain the volume and osmolality of body fluid constant despite wide variations in intake of salt and water.

Osmotic Pressure

Osmolarity is the attraction of water to particles and depends on the number (regardless of size or charge) of osmoles per litre of solution, hence it is temperature dependent. This value may be calculated from plasma concentrations of electrolytes, glucose, and urea: one of the most acceptable formulae is:

$$1 (\text{Na} + \text{K}) + \text{Urea} + \text{Glucose} \text{ (all values in mmol/L)}$$

The **osmolality** of a solution is the number of osmoles of solute per kilogram of solvent. This is most usefully expressed as milliosmoles per kilogram (mosm/kg). If osmolality cannot be measured, the specific gravity of urine provides an approximation. In the absence of glycosuria, proteinuria, or excretion of radiological contrast medium, the relation shown in table 1 applies. For simple pure solutions, i.e. NaCl, the difference between osmolarity and osmolality is so small that the two terms are effectively interchangeable. For

a more complicated solution, i.e. plasma, 10% comprises solids rather than water (protein, urea, lipids, glucose). Therefore osmolality is greater than osmolarity because of the smaller amount of water.

Although the movement of certain ions and proteins between the various body fluid compartments is restricted, water is freely diffusible. Consequently, the osmolality (total solute concentration) of all the body compartments is identical - normally, about 290 mosm/kg water. The solutes dissolved in body fluids contribute to total osmolality in proportion of their molar concentration. The main determinant of ECF osmolality is its Na⁺ content, whereas in ICF K⁺ salts are chiefly responsible. If ECF Na⁺ concentration (and osmolality) rises, water will be drawn from cells to re-establish equal osmolality. Conversely, acute hyponatraemia increases intracellular water regardless of the level of total body water (TBW). Sodium is unique as a solute in that changes in its concentration are most often due to changes in the volume of its solvent. Control of osmolality occurs through regulation of water intake (thirst) and water excretion (urine volume, insensible loss, and stool water), with the kidneys being the chief regulator. If water intake is low, the kidneys can reduce urine volume and raise urine solute concentration fourfold above plasma (1200 - 1400 mosm/kg water). If water intake is high, the kidneys can secrete a large volume of dilute (50 mosm/kg water) urine.

Only about 0.5% of plasma osmolality is attributable to colloids (molecular weight > 30.000). Normal colloidal osmotic pressure (COP) is 20-25 mmHg and is largely due to plasma proteins, although correlation between plasma albumin and COP is unreliable.

Normal water turnover and daily electrolyte requirements are shown in tables 1.2.2 and 1.2.3 respectively. Insensible water loss increases by 13% per degree centigrade increase in body temperature. The average loss of Na⁺ in sweat varies from 15 mmol/L (acclimatized to > 60 mmol/L (unacclimatized).

Types of Intravenous Fluids

These can be classified into two broad groups: colloid and crystalloid, with the crystalloid group further divided into resuscitation, rehydration, maintenance, replacement, special purpose type fluids, parenteral nutrition and "other" type fluids as recommended by the National Intravenous Infusion Rationalization Committee of South Africa.

Resuscitation

The clinical findings of a plasma-to-interstitial fluid shift of extracellular fluid are largely those of shock. The loss of Na⁺ and water and the accumulation of K⁺ in ECF are features of shock. Fluids used for resuscitation should therefore exert the same osmotic pressure as blood and should mimic the ECF in electrolyte composition. In hypovolaemic shock, the rapid transfusion of two litres of a balanced salt solution may be life-saving. The different types of resuscitation fluids are shown in table 1.2.4. Some workers have suggested that resuscitation fluids should incorporate an energy source in the form of dextrose. For this reason, Ringer lactate with dextrose 5% and sodium chloride 0.9% with dextrose 5% are available. In thermal injury, hypertonic salt solutions (240-300 mmol/L) are being used with increasing frequency as the initial resuscitation fluid to restore the extracellular sodium lost into the cells and into the eschar while infusing less water. Also, with respect to resuscitation

in trauma, major surgery, or shock, crystalloid solutions with packed red blood cells are more cost effective than the use of albumin.

Rehydration

Some rehydration fluids are shown in table 1.2.5. Mild dehydration is diagnosed on the history and clinical examination. Thirst and dryness of the mouth are present and suggests a +/- 4% loss of body mass, i.e. +/- 2.8 L (70 kg male).

The symptoms of moderate dehydration are marked thirst, dry mucous membranes and mild loss of skin elasticity. This indicates +/- 6% loss of body mass, i.e. 4 L (70 kg male). Severe dehydration is characterized by apathy, stupour, dry mucous membranes, skin laxity and signs of circulatory failure. This occurs with +/- 8% or more mass loss (approximately 5.6 L for a 70 kg male).

Some workers recommend 0.9% sodium chloride (Na+ 154 mmol/L) for the treatment of severe dehydration.

Maintenance

Maintenance fluid requirements are normally influenced by the basal metabolic rate. Typical daily losses in the adult are shown in table 1.2.2. The uncomplicated patient will require 2500-3000 mL of fluid daily. This volume is decreased in the presence of congestive cardiac failure, renal failure or other clinical conditions which predispose to fluid overloading.

Replacement

Replacement fluids are used to correct existing body fluid deficits and to replace ongoing abnormal losses, i.e. gastric drainage and intestinal oedema. For accurate replacement in the complex case and where mixed losses are occurring, samples should be analysed for electrolyte content. The composition of gastro-intestinal tract secretions are shown in table 1.2.8.

The "3rd Space" Effect

This is initiated by tissue damage which causes a transfer of isotonic fluid from functional body fluid compartments to non-functional ones, thereby becoming a non-functional appendage of the interstitial fluid. It remains sequestered for one to three days and is then gradually mobilized and excreted in the urine. This "3rd space" loss should be replaced with an isotonic balanced salt solution as listed under replacement solution. Replacement guidelines are as follows:

- Procedures with minimal loss of blood or fluids require no 3rd space replacement fluids
- Minimal trauma, replace 4 mL/kg/h
- Moderate trauma (hernia repair, appendicectomy), replace 6 mL/kg/h
- Extreme trauma (total hip replacement, radical mastectomy) replace 8 mL/kg/h

Fluid Therapy During Surgery

During surgery, considerable amounts of fluid may be required even if blood loss is not severe. Approximately 250 mL/hour of fluid is lost from exposed gut due to evaporation. Ventilatory support with dry gases accounts for a further loss of approximately 500 mL/24 hour. Fluid is also sequestered into the "3rd space" during surgery. The amount of balanced salt solution to be administered is approximately 10 mL/kg/h for major surgery and 3-5 mL/kg/h for minor surgery.

Postoperative Fluid Therapy

There is a tendency to retain both water and sodium in the postoperative period. Urine volume is low (approximately 400 cc/day) with a specific gravity up to 1020. Urinary Na⁺ excretion averages 5.20 mmol/day. During the first few days, the serum Na⁺ concentration falls (sodium paradox) due to dilution by water retention and Na⁺ entering the cells. The sodium paradox does not lower the serum Na⁺ below 125 mmol/litre. Na⁺ administration will not raise the low serum concentration of the Na⁺ paradox but may do so if K⁺ also is administered (to prevent Na⁺ entering the cells). When Na⁺ conservation ceases, Na⁺ is lost in the urine but the serum Na⁺ concentration rises (second sodium paradox) as Na⁺ re-enters the plasma from the cells and interstitial tissues (provided there is enough K⁺ available for normal intracellular K⁺ concentration). On the other hand, although K⁺ is excreted excessively in the urine (approximately 100 mmol/day), the serum K⁺ rises (K⁺ paradox) due to movement of K⁺ out of the cells. Based on the above metabolic response to injury, 3 L of fluid/day are recommended in the first 48 hours for adults following uncomplicated elective surgery. This should consist of 2 L of dextrose water 5% and 1 L of dextrose saline. After 48 hours, 3 L of maintenance fluids can be given (Electrolyte no 2 with dextrose 10% or adult Maintelyte solution). Orders for postoperative fluids must be based on a daily clinical assessment and laboratory results when indicated. It is unnecessary and potentially dangerous to administer K⁺ during the first 24 hours postoperatively, unless a definite K⁺ deficit exists.

Volume Disorders

Volume Deficit

Both water and electrolytes are lost from the extracellular fluid which becomes hypertonic partly due to insensible losses of water. Common disorders leading to ECF volume depletion include losses of gastro-intestinal fluids due to vomiting, nasogastric suction, diarrhoea and fistula drainage. Other common causes include sequestration of fluid in soft-tissue injuries and infections, peritonitis, intestinal obstruction and burns. Treatment is that of the underlying condition with replacement of the deficit and continuing losses with rehydration or replacement solutions. Water replacement may also be administered orally by nasogastric tube provided it can be absorbed. Replacement should take place slowly as to avoid cerebral oedema. Additional specific treatment may include continuous insulin infusion for diabetes mellitus and the intramuscular administration of aqueous vasopressin (5-20 iu twice daily) for diabetes insipidus.

Volume Overload

The metabolic response to injury favours sodium and water conservation by the kidneys independent of the ECF volume status. The tendency for water retention may be exaggerated if heart failure, liver disease, renal disease or hypoalbuminaemia is present. Clinical features include confusion, headache, cerebral oedema, convulsions and coma. The causes are increased fluid intake or inability to excrete water normally. Pathological hyperdipsia, excessive intravenous fluids and water absorption during bladder irrigation may produce water intoxication.

Inappropriate antidiuretic hormone (ADH) secretion, although an uncommon syndrome, is characterized by hyponatraemia with reduced plasma osmolality, elevated urine sodium concentration, normal ECF volume and normal renal and adrenal function. This syndrome may occur with head injury, chest infection and some cancers, i.e. carcinoma of the bronchus. The management of water overload is that of the underlying cause. In most cases, water restriction alone will be sufficient to correct the abnormality. Occasionally, if life-threatening central nervous system symptoms develop, hypertonic saline (1.8% NaCl) together with a diuretic (Furosemide) may be administered. In patients with inappropriate ADH secretion unresponsive to water restriction, the following may be considered:

- Demethylchlortetracycline
- Lithium
- Furosemide with high salt intake

Specific Electrolyte Disorders

Sodium (Na⁺)

About 25000 mmol of Na⁺ are filtered through the glomeruli daily, of which 70% is reabsorbed via the proximal tubules. Further reabsorption occurs passively in the thin segments of the loops of Henle and by an active process from the distal tubules and collecting ducts. Normal reference ranges of plasma sodium concentration are 135-145 mmol/L. Flame photometry measures the Na⁺ concentration in whole plasma and since about 6% of the plasma volume is occupied by lipid and protein which contains no Na⁺, the actual concentration in plasma water is higher. In clinical situations where the plasma lipid or protein is increased, "pseudohyponatraemia" may be produced. Ion-specific electrodes, which measure the activity of sodium ions in plasma water directly, are not affected by this problem.

Regulation of sodium concentration in plasma or urine is intimately associated with regulation of total body water and clinically reflects the balance between total body solute and total body water. Changes in K⁺ can also influence plasma sodium concentration. A fall in extracellular K⁺ concentration favours intracellular K⁺ moving passively into the extracellular fluid. Na⁺ (and to a lesser degree hydrogen) will enter the cells to maintain electroneutrality, thereby lowering plasma Na⁺ concentration. This initial fall in the plasma osmolality will inhibit release of antidiuretic hormone, resulting in increased water excretion and will return the plasma Na⁺ concentration back to normal. If, however, antidiuretic hormone secretion

cannot be reduced, then K⁺ depletion can lower the plasma Na⁺ concentration. With diuretic-induced hyponatraemia, volume depletion stimulates the release of ADH, and concurrent K⁺ depletion may contribute to the fall in plasma Na⁺ concentration towards normal. K⁺ supplements can also elevate the plasma Na⁺ concentration in normokalaemic patients. High extracellular concentrations of other effective solutes, i.e. glucose, raises the plasma osmolality and causes water to move out of the cells down an osmotic gradient lowering the plasma Na⁺ concentration by dilution. In comparison, urea is without effect on the plasma Na⁺ concentration, since it can easily cross the cell membrane.

Sodium Deficiency

Inadequate Na⁺ intake results in Na⁺ deficiency unless excessive losses are also present. Usually, there is concomitant water loss and patients are thus frequently referred to as being dehydrated. Symptoms include fatigue, muscular weakness, apprehension, diarrhoea, abdominal cramps, oliguria and convulsions. The plasma Na⁺ concentration is usually below 137 mmol/L with a urine specific gravity below 1010. In the absence of measurements of central venous pressure, the most reliable sign is a rapid change in mass. Management requires intravenous salt and water replacement. A 0.9% solution of NaCl is usually employed when the electrolyte concentration deficit is accompanied by a fluid volume deficit. The total Na⁺ deficit is calculated by multiplying the Na⁺ deficit by the approximate ECF volume (15% of adult body mass). In some severe cases, sodium chloride 5% in water solution is recommended. Each mL of this solution contains approximately 1 mmol of NaCl. Hypertonic NaCl solution should be administered intravenously at the rate of 1 mL/m² body surface/minute.

Sodium Excess

This may be secondary to renal sodium retention, cardiac and vascular disease, cirrhosis of the liver and miscellaneous causes, i.e. pregnancy, glucocorticoid excess and hypothyroidism. Symptoms include dryness of mucous membranes, elevated body temperature, depressed lacrimation, thirst and oliguria. The physical signs of Na⁺ overload are those of expansion of the intravascular or interstitial fluid compartments or both. Dextrose water 5% or balanced solutions provide free water to dilute the electrolyte concentration excess as they replenish maintenance amounts of electrolytes that may be required by the homeostatic mechanisms to re-establish the normal water-to-electrolyte ratio of 3.3 mL of water to each mmol of electrolyte. Before administering a solution that contains K⁺, one must ensure adequate renal function. Response to therapy can be monitored clinically and should ideally include weighing.

Potassium

The K⁺ in extracellular fluids constitutes only 2% of total body K⁺. The serum K⁺ concentration is determined primarily by the pH of extracellular fluid and the size of the intracellular K⁺ pool. As the pH rises, K⁺ moves into cells. A loss of 10% of total body K⁺ drops the serum K⁺ from 4 to 3 mmol/L at a normal pH. A fall in plasma pH of 0.1 causes a rise in plasma K⁺ concentration of approximately 1 mmol/L. Exercise may also induce a rise of K⁺ as much as 2 mmol/L in a minute.

The primary function of K^+ is its involvement with cellular enzyme activities. It also plays an important role in carbohydrate and protein synthesis. The difference in the concentrations of Na^+ and K^+ across cell walls determines the electrical potentials of cell membranes, and hence excitability and nerve impulse conduction.

Hyperkalaemia

The following factors must be considered in assessing the hyperkalaemic patient:

- Haemolysis, marked leukocytosis or thrombocytosis. Platelet counts greater than 1 million/mL may elevate the serum K^+ since the ion is liberated from platelets when clotting occurs
- The acid-base status should be assessed
- The rapidity of the elevated serum K^+ should be determined
- Iatrogenic causes must be excluded

Patients with severe trauma, burns, crush injuries, renal insufficiency, Addison's disease and marked catabolism are susceptible to hyperkalaemia. The main changes that occur with this condition are in muscle. Skeletal muscle becomes paralysed. In the heart, atrioventricular conduction time is diminished, followed by ventricular arrest or fibrillation. Classic ECG changes consist of ST segment elevation and peaked T-waves.

Hyperkalaemia is a medical emergency demanding immediate action (if ECG changes are present or serum $K^+ > 7$ mmol/L). In the absence of prerenal failure, treatment consists of:

- 20 mL 10% calcium gluconate intravenously over 5 minutes: this protects the heart from fatal arrhythmia
- 100 cc 8.5% sodium bicarbonate intravenously over 20 minutes: this produces alkalosis and decreases the serum K^+ level; however, Ca^{++} should be given first to prevent hypocalcaemia and tetany induced by a rapid rise in plasma pH from sodium bicarbonate administration
- 100 cc 50% glucose with 20 units of insulin intravenously as a single bolus followed by 20 g glucose and 6-20 units insulin per hour according to blood sugar
- cation exchange resins, i.e. Kayexalate 20-80 g/day (sodium polystyrene sulfonate) may be administered orally or rectally; it can be given with Sorbitol to encourage large bowel evacuation and enhance K^+ loss
- definitive treatment includes peritoneal dialysis or haemodialysis.

In non-emergency situations (serum $K^+ < 6.5$ mmol/L; no ECG changes), K^+ containing solutions should be discontinued and diuresis instituted.

The risk of developing hyperkalaemia in hospital remains at 1-2% and can reach 10% depending on the definition used. Potassium chloride supplements and potassium-saving diuretics remain the major culprits but they have been joined by newer agents i.e. salt substitutes, beta-blockers, converting enzyme inhibitors, non-steroidal anti-inflammatory agents, heparin and cyclosporine, among others.

Hypokalaemia

Potassium deficit, usually accompanied by hypokalaemia, can occur in a great variety of conditions. It can be caused by excessive loss of K^+ from the body, by increased use of K^+ by the body (2.7 mmol K^+ should be given/g nitrogen in the anabolic phase of recovery), and from decreased intake of K^+ . Electrocardiographic signs of low voltage, flattening of T-waves, depression of S-T segment and frequently a prominent U-wave indicate potassium deficit.

Urine K^+ excretion of more than 30 mmol/day associated with a serum $K^+ < 3.5$ mmol/L indicates renal potassium wasting. Diuretic therapy, alkalosis or increased aldosterone activity may be responsible. If renal K^+ excretion is less than 30 mmol/day, the kidneys are conserving K^+ and hypokalaemia reflects a total body deficit. Treatment consists of correcting the cause of hypokalaemia and administering K^+ . If the patient is able to eat, K^+ should be given orally, otherwise it should be given intravenously. Normally 80%-90% of the K^+ ingested is excreted in the urine, the remainder being excreted in the stools and perspiration. Adults on a diet adequate in calories but K^+ free may lose as much as 40 to 50 mmol of K^+ /day in the urine.

To obtain 50 mmol K^+ a patient would be required to eat three bananas or six oranges or three and a half cups of tomato juice or two cups of dried peaches - foods which may not be readily available. In patients with normal renal function, up to 40 mmol/L KCl is commonly added to intravenous infusion. Infusion rates generally should not exceed 10 mmol/hour or 120 mmol/day. Potassium chloride can safely be added to most intravenous solutions but it is incompatible with amphotericin, amikacin and penicillin G sodium. Adding KCl to a running infusion solution in flexible containers hanging in the in-use position has resulted in the pooling of KCl and a resultant high concentration bolus of the drug being administered to patients, with serious consequences. Extreme care must be taken to avoid extravasation. Concentrations greater than 80 mmol/L are more often associated with phlebitis. In urgent cases, as much as 40 mmol/hour and up to 400 mmol/day may be infused. Under these conditions, patients are best monitored in an intensive care unit. *If K^+ replacement is not accomplished with usual dosages, the patient should be assessed for magnesium deficiency. Diuretics increase renal magnesium excretion and when chronically administered, decrease intracellular magnesium levels.* This deficiency reduces active transport of K^+ into the cell and intracellular K^+ decreases irrespective of serum K^+ levels. In metabolic alkalosis, potassium chloride is specific since it helps to correct the acid-base abnormality as well as the hypokalaemia. Furthermore, a persistent hypochloraemic alkalosis suggests body K^+ deficiency.

Calcium

Calcium exists in the plasma in three forms - protein-bound (40-45%), ionized (50%) and complexed (non-protein bound, non-ionized 5-10%). The physiologically active form is the ionized form. Both dextrose water and solutions containing Ca^{++} must not be administered through the blood transfusion line because of the danger of pulmonary microemboli.

Hypocalcaemia

The most common cause is a low serum protein level. Patients experience no symptoms because the ionized fraction is normal. The "correction" of the plasma calcium may be simplified as follows: for every 1 g/L by which the plasma exceeds 40 g/L, 0.02 is subtracted from the total plasma calcium. A corresponding addition is made when the plasma albumin is less than 40 g/L. Other causes include hypoparathyroidism, hypomagnesaemia, osteomalacia, pancreatitis, renal disease, vitamin D deficiency, severe trauma, crush injuries and necrotizing fasciitis. The clinical manifestations are neuromuscular - hyperactive deep-tendon reflexes, a positive Chvostek sign, muscle and abdominal cramps, carpopedal spasm and convulsion. Electrocardiograph shown prolongation of Q-T interval.

Treatment is directed at correcting the underlying cause. In acute hypocalcaemia (myocardial function compromise) CaCl_2 5-10 mmol every six hours is recommended with a daily maintenance dose of 8 mmol/day. In non-emergency situations, 22 mmol calcium daily with vitamin D3 1.25 mgm twice weekly improves the condition. Aluminium hydroxyde gels to bind phosphate in the intestine also helps. Co-existing Mg^{++} or K^+ deficiency must be corrected as well.

Hypercalcaemia

Hypercalcaemia most frequently is caused by hyperparathyroidism, cancer with bony metastases, ectopic parathyroid hormone production, sarcoidosis, milk alkali syndrome and prolonged immobilization.

The symptoms and signs of hypercalcaemia include fatigability, anorexia, nausea, polydipsia and polyuria, deep bony pain, muscle hypotonicity, renal stones and coma. Treatment must correct dehydration and the electrolyte abnormality with 0.9% sodium chloride. Furosemida 20-40 mg intravenously every 4-8 hours produces a forced diuresis and reduces renal tubular and re-absorption of calcium. Phosphate also increases the movement of Ca^{++} into bone. Neutral phosphate 0.5-1.5 g/day should be given. If the patient is in coma, 50 mmol phosphate may be given intravenously over six to eight hours. Calcitonin (4MRC units imi 12 hours) is indicated in patients with impaired renal and cardiovascular function. Mithramycin 25 mgm/kg intramuscularly or intravenously and repeated every 24 hours is particularly useful for hypercalcaemia associated with metastatic cancer. Adrenal corticosteroids are useful for hypercalcaemia associated with sarcoidosis, vitamin D intoxication, and Addison's disease. When renal failure is present, haemodialysis may be required.

Magnesium

Magnesium is the fourth most abundant cation in the body. It is a key prosthetic ion in many enzymatic functions and is closely related to the other cations calcium, sodium and potassium. Disturbances in magnesium homeostasis occur in prolonged nasogastric secretion, parenteral feeding, and many disease states, i.e. alcoholism, short-bowel syndrome and other disorders with steatorrhoea.

Hypomagnesaemia

The clinical manifestations resemble those of hypocalcaemia since magnesium deficiency interferes with the action of thiamine; some of the neuropsychiatric manifestations may be related to this. The diagnosis of hypomagnesaemia depends on clinical suspicion with confirmation by measurement of the serum magnesium. In moderate magnesium deficiency, oral magnesium sulfate replacement is adequate. In more severe deficits, parenteral magnesium must be administered intravenously (20-40 mmol MgSO₄/L of solution). Two cc of 50% magnesium sulfate provides 8 mmol Mg⁺⁺ (table 12). The ECG should be inspected for prolongation of the Q-T interval. Magnesium should be given cautiously to oliguric patients and through central venous pressure lines. The recommended daily maintenance dose is 15-20 mmol Mg⁺⁺/day. If magnesium sulfate is used intramuscularly, it is probably best to give in two separate depots.

Table 1.2.12. Solution additives

| |
|---------------------------------------------------------------------------------------------|
| 1 g NaCl = 17 mmol Na ⁺ |
| NaCl 5% 1 L = 855 mmol Na ⁺ |
| 1 g KCl = 13 mmol K ⁺ |
| 1 mL 8.5% NaHCO ₃ = 1 mmol NaHCO ₃ |
| KCl 20% 10 mL ampoule 1 mL = 2.5 mmol K ⁺ |
| MgSO ₄ 50% 2 mL ampoule 1 mL = 4 mmol Mg ⁺⁺ |
| CaCl ₂ 10% 10 mL ampoule 1 g = 2.2 mmol Ca ⁺⁺ |
| K ₂ PO ₄ 20% 10 mL ampoule 1 mL = 2 mmol PO ₄ ⁻ |

Hypermagnesaemia

Hypermagnesaemia usually occurs in patients with renal disease. The initial signs and symptoms are lethargy and weakness. Electrocardiographic changes resemble those in hyperkalaemia (widened QRS complex, S-T segment depression and peaked T waves). Loss of deep-tendon reflexes and coma are bad prognostic signs. Treatment of hypermagnesaemia consists of giving intravenous 0.9% sodium chloride to increase the rate of renal magnesium excretion. Ca⁺⁺ infusion should be given to antagonize some of the neuromuscular actions of magnesium. Patients with severe renal disease may need dialysis.

Phosphorus

Hypophosphataemia

The most frequent causes are infusion of carbohydrate solutions, gram-negative septicæmia, liver disease, alcohol and antacid administration. Phosphorus has been shown to play an important role in the three vital steps of oxygen delivery: adequate alveolar gas exchanges, perfusion of tissue with oxygenated blood and release of oxygen from haemoglobin. Parenteral feeding regimens should provide approximately 100 mmol potassium dihydrogen phosphate per 1000 kilocalories. If severe hypophosphataemia develops in a patient on total parenteral nutrition, the safest course is to stop the infusion of the nutrient solution. Large amounts of phosphate are lost from the body during the development of ketoacidosis, with deficits of up to 320 mmol reported. As with K⁺, plasma levels of phosphate at the time of presentation in ketoacidosis may be low, normal or high, but in association with insulin therapy phosphate returns intracellularly and produces hypophosphataemia which is often pronounced. However, phosphate supplementation does not influence the clinical course of ketoacidosis. There is also the potential danger of lowering the plasma Ca⁺⁺ levels secondary to phosphate infusion. Therefore, *phosphate treatment is not recommended in the management of ketoacidosis.*

Hyperphosphataemia

Hyperphosphataemia most often develops in severe renal disease, after trauma or with marked tissue catabolism. It is usually asymptomatic. Because it raises the calcium-phosphorus product, the serum calcium concentration is depressed. Iatrogenic hyperphosphataemia may be associated with symptomatic hypocalcaemia. Treatment of hyperphosphataemia is by diuresis, the administration of phosphate-binding antacids, i.e. aluminium hydroxide gels and dialysis in patients with renal failure.

Comment

Fluid and Electrolyte Therapy

W L Michell

It is a tribute to human physiology that a wide variety of perioperative fluid management regimens are currently practised with apparent little adverse effects on the average surgical patient.

In the early 1950s an awareness of stress response of salt and water retention resulted in a policy of prescribing limited quantities of 5% dextrose to postoperative patients. The physiological adaptive mechanisms that comes into play following trauma were evolved over millions of years to enable the injured animal to survive moderate injury until sufficiently covered to forage. These mechanisms may be counterproductive in hospitalized patients with access to intravenous fluids.

In the 1960s fluid policies changed when Tom Shires demonstrated that during shock the ECF was depleted by fluid sequestration. Failure of the cellular membrane ATP Na⁺-K⁺

pump results in the movement of sodium and water into cells. Provided sufficient large quantities of fluid are administered, and ECF deficit is restored, the obligatory salt and water retention can be largely overcome. This approach and the development of the intravenous canulae and fluid market liberalized from earlier restrictive approach and patients were sometimes subjected to massive infusions of water and sodium. The pendulum perhaps swung to far.

Despite adequate fluid replacement, other stimuli (pain and fear) result in some salt and water retention, and patients with cardiac and renal disease, with a limited ability to excrete sodium, are susceptible to fluid overload and pulmonary oedema.

A wide variety of intravenous solutions are available on the market - not all are ideally suited for their proposed function. Resuscitation and rapid replacement of fluid are best accomplished by a solution with an electrolytic composition similar to ECF, i.e. high sodium, low potassium and without glucose. Rapid administration of glucose-containing fluids to a shocked patient will cause hyperglycaemia, forced diuresis and hyperosmolar coma. "Maintenance" type fluids containing glucose and higher concentrations of potassium should be infused at a slower, steady rate to allow metabolism of the glucose and the movement of K⁺ into the cells. These solutions have a high osmolality and, to prevent peripheral vein irritation, are best infused through a central line - if the central venous pressure is being monitored.

The choice of fluid for resuscitation - whether crystalloid or colloid - remains controversial. Colloid solutions are supposed to remain in the intravascular compartment while crystalloid solutions are distributed throughout the ECF. Approximately three times the intravascular volume deficit must be infused when replacing with crystalloids. Crystalloids are favoured for the early resuscitation phase because of their ready availability, cheapness and safety. Although clinical trials have shown that pulmonary oedema is less likely following resuscitation with crystalloid, many clinicians are concerned about the over-expansion of the interstitial space and the effect this may have on cellular oxygenation. Reversal of shock can be achieved more rapidly and with less volume using colloids. On the other hand, colloids are expensive and carry special risks: infection (albumin solutions), coagulation defects and cross-matching difficulty (dextrans), and allergic reactions (all).

The surgical patient of today is older and more chronically ill than ever before. Optimal fluid management depends upon frequently reviewing individual fluid prescriptions and careful monitoring of biochemical and, above all, clinical parameters.

Chapter 1.3: Blood Transfusion and Its Hazards

P Bauling

Introduction

Blood transfusion as a mode of therapy represents a **double-edged sword**. On the one hand it may represent a life-saving intervention and indeed has saved many lives since Landsteiner's work paved the way for clinical blood transfusions in 1900. On the other hand it has become one of the most feared and dreaded therapies in recent years, mainly due to the

infectious risks involved (HIV-Aids, Hepatitis B, non-A and non-B Hepatitis). It thus behoves the clinician to weigh carefully the risk benefit ration in each and every individual case where he contemplates the use of transfusions. Furthermore the surgeon should possess extensive knowledge of this frequently used but dangerous mode of therapy.

What Blood Products are Available?

1. Whole blood
 - stored
 - fresh, warm
2. Red cells
 - ordinary packed cells
 - leukocyte poor
 - washed red cells
 - stored, frozen red cells
3. Fresh frozen plasma
4. Freeze-dried plasma
5. Platelet cream
6. Single-donor platelet concentrate
7. Cryprecipitate (F VIII)
8. Freeze-dried F VIII.

A detailed description of each of these products is beyond the scope of this chapter. A detailed discussion such as that by P. J. Coghlan needs to be studied by each clinician administering blood products to patients.

How is Blood Stored and What Changes Occur During Storage?

Whole blood is collected into closed plastic bags mixed with an anticoagulant and stabilized to a final volume of approximately 500 mL (70 mL preservative and 430 mL whole blood). Acid citrate dextrose (ACD) has been the traditional solution used since the Second World War but more recently there has been a move towards solutions with added phosphate and adenine (citrate-dextrose-adenine) (CPD-A) to increase post-transfusion viability and red cell function (i.e. 2,3 diphosphoglycerate levels). Blood should be stored at 4 °C in a

refrigerator specifically designed for the purpose. Blood may be stored for up to 35 days with CPD-A.

Effects of Storage on Blood

Like any biological fluid, blood degenerates with time during storage. Changes occur in both the cellular and the plasma components. Intracellular ATP becomes depleted during storage. Cell membrane damage occurs with rigid spherocyte formation, swelling and, finally, potassium leak. Parallel to these changes, haemoglobin function may be altered due to falling levels of both ATP and more significantly, 2,3 diphosphoglycerate (2,3 DPG) resulting in increasing oxygen affinity. These changes occur earlier and to a greater extent in whole blood than in red cell concentrates. Platelets and granulocytes are responsible for the formation of microaggregates, with various cell-damaging enzymes being released into the storage medium.

When Should Blood Products Be Used?

Fresh Warm Blood

It is debatable whether the benefits ever out-weighs the risks in this particular therapy.

Indications

- After massive transfusion with ongoing bleeding and complex haemostatic defect(s).
- Rh incompatibility in the newborn where the risk of kern icterus is substantial.

Risks

HIV (Aids), Treponema pallidum, malaria, other bacteria.

Banked Whole Blood

- Type and cross matched.
- Type specific blood.
- O Rh negative (red label).

Once again the emergent clinical situation will determine the use of red label or type specific blood, and its use should be avoided as far as possible for the obvious reason of possible allergic transfusion reactions.

Red Cells

The widespread introduction of blood component therapy as a concept has been advantageous to clinician, patient and blood banking institutions. The most frequently used product is packed cells in one of its four forms:

- Ordinary packed cells.
- Washed red cells.
- Leukocyte-poor red cells.
- Frozen red cells.

Of these, ordinary packed cells are the most frequently used blood product.

The concept that the loss of whole blood should be replaced by whole blood has had to be examined in the face of increasing demand for blood products.

The primary purpose of a red-cell transfusion is to increase the oxygen-carrying capacity of the blood. In assessing the need for a red-cell transfusion the factors to be taken into account should include:

- an estimate of the extent of red cell loss
- the rate of red cell loss, and whether such loss is likely to occur
- the oxygen requirements of the patient
- whether the patient can compensate for the reduction in haemoglobin by increasing ventilation and perfusion
- the desired rate of restoration of oxygen-carrying capacity.

The decision to infuse whole blood or red-cell concentrate is therefore dependent on a proper assessment of the patient's need and the requirement for blood volume expansion. Red cell replacement is probably not indicated in the non-emergency, pre-operative situation where haematinic therapy would be safer and as effective. It is also not in the patient's interests to attempt to normalize the peripheral blood count by way of transfusions without considering the indications for other red cell preparations as shown in table 1.3.1.

Other blood products are indicated by specific needs:

Fresh Frozen Plasma (FFP)

- Coagulation abnormalities.
- Burns.
- Immoglobulin deficiencies.
- Factor V and VIII deficiency.

Note

- The practice of using FFP as a volume expander is questionable, as other options are available (unless coagulopathies may also loom as a possibility).

- The use of FFP to raise serum protein values is also a practice that should be discouraged as it delays the more obvious therapeutic decision namely that of full nutritional support.

Cryoprecipitate

- Haemophilia A.
- Von Willebrand's disease.
- Fibrinogen deficiency of DIC.

Dried Plasma

- Emergency volume expander.
- Burns.

Platelet Cream

- Postcardiopulmonary bypass.
- Severe DIC.
- Post-chemotherapy for cancer.
- Massive transfusion syndrome.
- ITOP *with* life-threatening haemorrhage.

Note

- Despite this list of indications for platelet transfusions, objective clinical and laboratory criteria for the administration of platelet transfusions are still lacking.

- Platelet administration in ITP should be given only to arrest haemorrhage, as platelet survival is reduced to a few hours in this condition.

How is Blood Ordered?

Medico-legally the clinician must collect a sample of blood, label it himself and request the necessary blood products. He should also be present or nearby when the first unit is started. Furthermore a personal visit to the local blood bank by the clinician to familiarize

himself with local practices, terminology, etc. helps to prevent catastrophic misunderstandings. Finally, the clinician carries full responsibility with regard to the administration of blood and blood products and thus should verify that the correct blood product is administered safely and correctly.

How is Blood Given?

- Via large-bore intravenous canula.
- Appropriate filter(s) should be used.
- Blood should be warmed - to 37 °C.
- Qualified nursing supervision or physician's presence is mandatory.
- Immediate intervention if undesired reactions are encountered or even suspected.
- BP, pulse, temperature to be recorded every 30 minutes at the initiation of each unit.

What are the Risks of Blood Product Administration?

Risks of Massive Rapid Transfusion (> 10 U/24h)

There are several potential problems related to massive, rapid blood transfusions. These are often associated with critically ill patients and it is therefore difficult to assess the contribution of blood transfusion to the conditions listed here:

Citrate Toxicity

- Infusions > 500 mL/10 minutes.
- Calcium chloride to be administered after every 5 units.
- FFP every 5 units.

Acid Load

- Seldom needs therapy.
- Assess blood pH during severe metabolic acidosis of shock (blood gases).

Hyperkalaemia

- Seldom needs therapy except in renal failure patients.

Hypothermia

- Extremely important to warm blood during rapid infusions (to warm 1 U blood from 4 °C to 37 °C requires 13000 kilojoules = one hour of heavy muscular activity).

Jaundice

- Common: conjugated hyperbilirubinaemia due to delay in excretion of conjugated product from hepatocyte to bile canaliculi causes haeme load; also occult incompatibility of one or more units, haematoma absorption, haemolysis, removal of old and damaged cells in transfused blood (20-30%).

Other Potential Hazards of Massive Transfusion

- Micro aggregates (impaired oxygenation).
- Fluid overload.
- ARDS.
- Multiple organ failure.
- Haemostatic failure.
 - Dilution.
 - Depletion.
 - DIC.
- RES blockade.
- Sodium overload.

Other Risks of Blood Component Therapy

Blood component therapy may be responsible for a wide range of adverse transfusion reactions:

Pyrexia

Mild febrile reactions are not usually a matter for concern. However, rigors and pyrexia in critically ill patients should never be considered as harmless and temperature above 38 °C should not be ignored. The majority of febrile reactions are now regarded as being due to an immunologic reaction against one or more of the transfused cellular or plasma components, usually leukocytes.

Mononucleosis Syndrome

This is the development of a swinging pyrexia with varying degrees of atypical peripheral blood monocytes. The temperature may fluctuate markedly with associated rigors and drenching sweats, but the patient may feel reasonably well between febrile attacks. Abnormalities in liver function are common. The syndrome is probably due to cytomegalovirus.

Acquired Immunodeficiency Syndrome (AIDS)

The most recently recognized infectious complication of blood transfusion is the acquired immunodeficiency syndrome. Understanding of this retro virus infection is still evolving. Bloodbanks in SA now routinely test every unit of donated blood for HVI.

Haemolytic Reactions

Clinical features of haemolytic transfusion reactions are:

- Initial symptoms and signs

Acute intravascular haemolysis, which is more typical of ABO incompatibility, may manifest in several ways. The classic symptoms and signs of an acute haemolytic transfusion reaction include apprehension, flushing, pain (infusion site, headache, chest, lumbosacral and abdominal), nausea, vomiting, rigors, hypotension and circulatory collapse.

- Haemostatic failure

A haemorrhagic diatesis due to disseminated intravascular coagulation may be a feature, resulting in severe generalized haemostatic failure with haemorrhage and oozing from multiple sites. As the responsible transfusion is likely to have been administered for haemorrhage, increasing severity of local bleeding may be the first clue to an incompatible transfusion, especially if the patient is anaesthetized.

- Oliguria and renal impairment

Renal impairment may complicate a haemolytic transfusion reaction and prevention or appropriate management of established renal failure is a crucial part of therapy. If circulating volume and urinary output are rapidly restored, established renal failure is unlikely to occur.

- Anaemia and jaundice

A severe haemolytic transfusion reaction may be suspected from the development of jaundice or anaemia.

Allergic and Anaphylactic Reactions

Plasma may cause reactions ranging from mild pruritus, erythema and urticaria to a fulminant fatal anaphylaxis. Within this spectrum of reactions, severe flushing, hypotension, fever, angioedema and bronchospasm may occur.

Suppression of the Immune System

A generalized immunosuppressive effect of blood transfusion, well known to transplantation surgeons and immunologists, does exist. The role of this effect in particularly cancer surgery is at present debated in the literature.

Presentations of transfusion reactions are depicted in table 1.3.2.

Table 1.3.2. Presentations of transfusion reactions

- Rigors, chills, pyrexia
- Pain (chest, back, abdominal, local)
- Respiratory distress, tachypnoea, cyanosis
- Hypotension and peripheral circulatory failure
- Haemoglobinuria, oliguria or anuria, renal failure
- Jaundice
- Allergy, skin rash, pruritus, anaphylaxis
- Bleeding, bruising, purpura
- Thrombophlebitis
- Abnormal laboratory test results:
 - Hyperbilirubinaemia
 - Reduced haptoglobins
 - Coagulation abnormalities
 - Thrombocytopenia

How are These Events Managed?

Rapid massive transfusion, particularly during anaesthesia, requires a keen awareness of the hazards involved and early or anticipatory measures to deal with the problems listed above.

Acute allergic and/or haemolytic reactions need to be recognized early and treated aggressively:

- Stop infusion
- Remove drip line
- Infuse saline
- Note and record all reactions
- Notify and return blood to blood bank along with documentation of reaction
- Treat symptomatically
- Support cardiorespiratory system
- Ensure high urine flow
- Treat allergic reaction (antihistamines, corticosteroids)

What Lies in the Future?

The administration of blood products from centralized blood banks has become a topic of discussion due to the worldwide AIDS risk. Already opportunities have been created for individuals to store their own blood for extended periods in case of need. Others travel around the world with "safe" blood as luggage.

Transfusion of autologous blood will eliminate the risks of homologous blood from donors. With increasing concern about post-transfusion infections and immune reactions, there is likely to be a greater interest and emphasis on this kind of transfusion therapy. There are three options in the use of autologous transfusion:

Preoperative Collection

Blood is collected from the patient at intervals in the weeks prior to elective surgery and stored as whole blood. Alternatively, but less economically, blood may be collected months before surgery and stored as whole blood or frozen red cells. The latter approach is only used for patients with rare blood groups. There are several logistic problems in preoperative collection, and the patients are frequently too unwell or anaemic for such an approach to be safe. However, patients undergoing elective vascular surgery who are mildly polycythaemic are ideal candidates.

Peri-Operative Haemodilution

Up to three units of blood is collected immediately prior to surgery with simultaneous infusion of colloid (i.e. albumin or dextran 70) in order to lower the haematocrit to about 30%. Retransfusion of autologous blood is started when intraoperative loss exceeds 300 mL. Blood loss of up to 1.5 L can be replenished in this way and additional homologous blood is seldom needed. This technique is contraindicated in patients with cardiac disease.

Intra-Operative Autologous Blood Salvage

Rapid, massive blood losses can occur in vascular surgery, surgery for liver trauma and ectopic pregnancy. Intraoperative salvaging of autologous blood may be useful in these situations if the appropriate technology and expertise is available.

Extensive research into molecular, synthetic haemoglobin solutions and other solutions (soluble fluorocarbons) capable of O₂ transport, are under way but have not reached the point of wide-spread clinical utilization.

Comment

Blood Transfusion and Its Hazards

P H K Cilliers

Since blood transfusion is a double-edged sword, which may save a patient's life or lead to life-endangering reactions and complications, it should be administered judiciously. The physiologic basis for the use of whole blood or red blood cell concentrates should thus be understood by all clinicians. In short it is used to restore or maintain the patient's oxygen-carrying capacity to enable normal oxygen delivery at cellular level. Gould et al. state that the traditional determinants of oxygen transport are pulmonary gas exchange, blood flow, haemoglobin mass and haemoglobin-oxygen affinity.

To determine the need for blood transfusion, the mechanisms of normal oxygen transport should be understood.

The Basic Physiologic Principles of Oxygen Delivery

- Oxygen Delivery = Cardiac Output x Arterial Oxygen Content
- Oxygen Consumption = Cardiac Output x (Art - Mixed Ven O₂ Content)
- Oxygen Content = (Haemoglobin x Saturation) / (0.0031 x PO₂)
- Saturation of haemoglobin depends on PO₂ and the haemoglobin-oxygen affinity (the well-known sigmoid oxygen-dissociation curve)
- Oxygen Extraction Ratio = Oxygen Consumption / Oxygen Delivery

Under normal conditions this is 0.25; i.e. the available oxygen is four times the normally consumed oxygen.

- Cardiac output increases with normovolaemic haemo-dilution due to decreased blood viscosity and increased minute volume, while at cellular level the oxygen consumption increases. It has been shown by Gruber and Messmer that oxygen delivery increases with a falling haematocrit with optimal delivery at a value of 30%. Only when the haematocrit falls below 25%, will the oxygen delivery start to decrease. Thus, it is obvious that blood transfusion can be withheld and due to the inherent dangers should only be given if really necessary.

Autologous Blood Transfusion

When it is decided that blood is or probably will be needed, the possibility of giving autologous blood should be contemplated.

Homologous Blood Transfusion

Reactions due to homologous blood transfusions can easily be grouped under the following headings.

Immediate Transfusion Reactions

1. Reactions in which blood may be continued.

- Allergic reactions.
- Mild febrile reactions.

2. Reactions in which blood must be stopped.

- Severe febrile reactions.
- Haemolytic transfusion reactions.
- Delayed haemolytic reactions.

Late Transfusion Reactions

1. Isosensitization.

2. Disease transmission.

- HIV (AIDS).
- Serum hepatitis.
- Brucellosis.
- Malaria, etc.

Reactions Due to Massive Transfusions

1. Hypothermia.
2. Citrate intoxication.
3. Hyperkalaemia.
4. Acidosis.
5. Hyperammonaemia.
6. Coagulation defects - decreased platelets and labile clotting factors.
7. Post-transfusion lung syndrome.

Recent Developments

Preservatives

A change from acid-citrate-dextrose (ACD) to citrate-phosphate-dextrose (CPD) whereby the acceptable length of storage is increased from 21 to 28 days and the function of the red blood cells is improved during the early days of storage due to better preservation of levels of 2,3-diphosphoglyceric acid (2,3-DPG). Newer modifications, CPDA and CPDA₂, are still being evaluated.

Red Cell Substitutes

- Halogenated Hydrocarbons.

These are synthetic oxygen-carrying agents such as perfluorocarbons with intermediate-length branched or cyclic carbon skeletons which have been used extensively in Japan. Problems associated with their use are mainly that only three times more oxygen is delivered than with plasma and the relationship between oxygen content and oxygen tension is a straight line and not sigmoidal. The implication is that high oxygen percentages must be inspired to attain an arteriovenous difference in oxygen tension of about 500 mmHg.

- Stroma-Free Haemoglobin

This substitute has several highly desirable properties, namely the augmented oxygen-delivering properties expressed in the sigmoid-shaped curve; as a protein solution it has plasma-specific osmotic activity; no need for crossmatching and apparently no transmitting of infections. However, it is rapidly excreted in the urine with a short intravascular half-life.

Summary

Blood is still a life-saving agent, but due to the various problems associated with its use, should only be given when it is really needed. To use this valuable agent a clear

understanding of the basic underlying physiologic principles is mandatory. If possible, autologous blood should be used. Whenever homologous blood is used, knowledge of the possible adverse reactions and their treatment is necessary. It is also expected that the clinician should be aware of new scientific developments and products which might replace blood usage in the future.

Chapter 1.4: Antimicrobial Agents and Infection

W Sielling

Antimicrobial Agents

These agents are used by surgeons under two distinct sets of circumstances, i.e., prophylaxis and therapy. The toxicity, activity against microbes and kinetics are the three most important aspects of these drugs.

The Beta Lactam Antibiotics

Four major classes of this group are identifiable, i.e.:

- Penicillins
- Cephalosporins
- Carbapenems and
- Monobactams.

The Penicillins

These agents consist of a beta lactam and a thiazolidine ring with a variable side chain. The mode of action is through binding to penicillin-binding proteins (PBP), inactivating their transpeptidase activity and in doing so, synthesis of the peptidoglycan layer of bacteria. PBP class affinity varies decidedly between different beta lactam antibiotics. Resistance to the beta lactam antibiotics therefore rests on permeability variance, decreased PBP binding and destruction or inactivation by beta lactamases; these are also drug specific. These beta lactamases are encoded either on the organisms's own DNA or plasmids.

Pharmacology

The serum half-life of all the penicillins vary between 0.5 to 0.8 hours, being longest for Piperacillin at 1.3 hours. Procaine pen G has a half-life of approximately six hours and benzathine pen G three weeks representing the two major repository forms of the drug. Renal tubular excretion is the major route of elimination, biliary elimination only being truly important in the case of nafcillin and the antipseudomonal penicillins. Probenecid blocks excretion and prolongs half-life of all the penicillins (with a creatinine clearance of less than 10 ml/min dosage must be halved). As dialysis removes major amounts of penicillin from serum, dosage after dialysis must be instituted. Urinary concentrations of all penicillins are

high. Allergic reactions constitute the vast majority of adverse reactions to penicillins. The immediate type hypersensitivity reactions may be life-threatening and are contra-indications to the use of all penicillins. It must be borne in mind that 10% of these patients demonstrate cross reactions on cephalosporin administration. Reactions classified under this heading include anaphylaxis, bronchospasm, glottisoedema and urticaria. Other skin rashes and gastroenteritis are not absolute contra-indications to therapy with penicillins. Neutropenia, Coombs positive hemolytic anaemia and platelet aggregation inhibition (carbenicillin) are included in the potential side effects. Eosinophiluria due to an interstitial nephropathy occurs mainly with methicillin therapy, whereas massive doses of penicillins may provoke seizure activity.

The Ordinary Penicillins

This group of drugs includes parenteral penicillin G as well as oral pen V (an acid stable penicillin formulation for oral administration only). This group of drugs is highly active against *Streptococcus pyogenes* and penicillin susceptible *Streptococcus pneumoniae* and sensitive *Neisseria gonorrhoeae*, as well as *Neisseria meningitidis*. Therapy of the enterococci and *Listeria* makes a combination with an aminoglycoside essential. *Bacillus anthracis* and *Corynebacterium diphtheriae* remain highly susceptible, while the vast majority of staphylococci are not adequately treated with these compounds. Of the anaerobes *Peptostreptococci*, *Actinomycetes*, *Bacteroides melaninogenicus*, *Fusobacterium* and *Clostridium* are sensitive to therapy, while gram negative anaerobes remain resistant. *Treponema pallidum* is sensitive to this antibiotic.

Penicillinase Resistant Penicillins

This group of compounds is active against *S. pyogenes* and *S. pneumoniae*, but not *S. faecalis*. Its main use is against penicillin-resistant, methicillin sensitive *Staphylococcus aureus* in a dosage of 4-12 g daily for adults divided into four to six daily doses. No anaerobic or gram-negative activity worth mentioning is attributed to this group of agents. Nafcillin and methicillin are not used in South Africa, while oxacillin may be administered orally or parenterally. Cloxacillin is very similar to oxacillin as it dicloxacillin and flucloxacillin.

The Aminopenicillins

This group of agents demonstrated much the same antibiotic spectrum as the natural penicillins, but is more active in-vitro against the enterococci and *Listeria*. In therapy of these two species it is still considered necessary to add an aminoglycoside. *Haemophilus influenzae* and *Haemophilus para-influenzae* are often susceptible. Community acquired *E. coli* strains are still susceptible to this antibiotic, but most of the other gram negatives are resistant.

Amoxicillin is absorbed significantly better than ampicillin and blood levels are considerably higher.

Hetacillin, pivampicillin, becampicillin, talampicillin and epicillin are some of the other aminopenicillins.

The Antipseudomonal Penicillins

Carbenicillin was the first of these compounds, but is rarely used now, due to the high accompanying sodium load. Of this category of penicillins, the only one used therapeutically is an ureidopenicillin, i.e., piperacillin. It has excellent activity against streptococci, *Neisseria* and *Hemophilus* as well as many of the *Enterobacteriaceae* (*E. coli*, *Klebsiella*, *Proteus*, *Enterobacter*, etc.). It is highly active against *Pseudomonas*, but it is widely accepted that combination with aminoglycosides is wise.

The Cephalosporins

In this case the beta lactam ring is attached to the dihydrothiazine ring. The attachment of different chains to position 7 of the molecule is responsible for changes in antibacterial activity, while substitution at position 3 is responsible for changes in pharmacokinetic and metabolic characteristics. Seven different binding proteins exist with differing effect on peptidoglycan synthesis and bacterial morphology. Cephalosporins are classified within generations on the basis of antibacterial activity. None of the cephalosporins can confidently be prescribed for methicillin-resistant *S. aureus*. Side effects are similar to those of penicillins. Allergic cross reaction occurs in about 10% of patients and in patients with immediate hypersensitivity reaction extreme caution should be exercised. As with penicillins, with few exceptions mild to moderate dosage adjustment is necessary in renal failure.

First-Generation Cephalosporins

This group of drugs include cefazolin, cephalexin and cephadrine (Cefril)(parenteral drugs with a half-life of approximately one and a half hours). Cephalothin (Keflin) and cephapirin by contrast are parenteral drugs with a half-life of just more than half an hour. Cefadroxil (Duracef), cephadrine (Cefril) and cephalexin (Keflex) are oral preparations with a half-life of approximately half an hour.

The spectrum of activity includes *S. pyogenes*, *S. pneumoniae*, and *S. agalactiae*, but exclude many of the viridans group streptococci as well as the enterococci. Reasonably good activity exists against *E. coli*, *K. pneumoniae* and *P. mirabilis*. Anti-anaerobic activity is similar to that of the natural penicillins, and also excludes *B. fragilis* from its spectrum. This category of drugs cannot be utilized for *N. meningitidis* infections due to inefficient blood brain barrier penetration.

Second-Generation Cephalosporins

Cephmandole (Mandokel), cefocitin (Mefoxin), cefaclor (CeClor) and cefuroxime (Zinacef), are the most widely applied drugs of the category and have a half-life of approximately fifty minutes barring the ninety minutes of cefuroxime. Cefonicid and ceforanide have half lives of 260 and 180 minutes respectively. Gram-negative spectrum is wider than that of the first-generation congeners. *E. coli*, *Klebsiella spp.* and indole positive *Proteus spp.* are more sensitive. A propensity of cephmandole to induce resistance to itself and other drugs in *Enterobacter* and *Citrobacter spp.* and in nonsusceptible *Serratia* and *Pseudomonas* strains, exists, via beta lactamase induction.

Cefoxitin (Mefomi) has a remarkable anti-anaerobic potency, including *B. fragilis* subspecies, and is more active against *Serratia*, but also can induce beta lactamases, as is the case for cefamandole (in the same genera).

Cefaclor (CeClor) is an oral preparation more active than first-generation drugs against *H. influenzae* (excluding some beta lactamase producers), *E. coli* and *P. mirabilis*. Cefuroxime (Zinacef) is similar to cefamandole, but penetrates CSF adequately to be effective in therapy of susceptible *H. influenzae*, *N. meningitidis* and *S. pneumoniae* strains.

Third-Generation Cephalosporins

The half lives of cefotaxime (Clafrian), ceftriaxone, moxalactam, cefoperazone and ceftazidime are 65, 480, 60, 110 and 260 minutes respectively. Cefotaxime has good gram positive activity excluding enterococci and *S. aureus* as well as *S. epidermidis*. *L. monocytogenes* is likewise not effectively treated by this compound. Gram negatives, excluding pseudomonas, are very effectively treated with this compound. As with other drugs of this category, concern remains in treating organisms with inducible beta lactamases with single agents. Anaerobic cover is similar to that of the first-generation cephalosporins, excluding effectivity against the majority of *B. fragilis* isolates.

Ceftriaxone (Rocephine) is virtually identical microbiologically to cefotaxime, but the long half-life makes single or double daily dosing practical policy.

Moxalactam has lapsed into virtual obscurity due to its effect on the production of certain coagulation factors, with a resultant bleeding tendency.

Cefoperazone is much less active than cefotaxime against gram negative anaerobes excluding *P. aeruginosa*, but is more active against *S. aureus*. Anaerobic efficacy is similar to that of cefotaxime.

- Cefrazidime (Fortum) is less active than cefotaxime against gram-positive aerobes, but it is similar to cefotaxime on all other counts barring its godd activity against *P. aeruginosa*. In the therapy of this organism, however, combination therapy is advised by many authors.

Thienamycin

Imipenem is a combination of cilistatin (a renal tubule dihydropeptidase inhibitor) and N-formimidoyl thienamycin (the antibiotic). The addition of cilastatin prevents renal inactivation and so doing nephrotoxicity and improves urinary availability. The drug acts by binding to one of the penicillin-binding proteins and is very stable to beta-lactamase mediated hydrolysis. This drug penetrates all tissue and other fluid compartments well. The half-life is approximately one hour. As excretion is renal, mild dosage adjustments is necessary in patients with renal failure. Leukopenia and ostensibly unimportant enzyme elevations have occasionally been reported. The combination drug is not nephrotoxic.

The spectrum of activity of this drug is such that virtually all pathogens are covered including gram-positive and negative organisms as well as anaerobes. Notable exceptions are the enterococci. In the therapy of *Pseudomonas* it seems probable that this agent can be used as a single agent.

Monobactams

Of this group of agents only azthreonam can be expected on the South African market in the immediate future. Chemically it is a monocyclic beta lactam. It has very little gram positive or anaerobic activity. The *Enterobacteriaceae* and *Pseudomonas spp.* excluding *P. cepacia* and *P. maltophilia* are sensitive to this organism. Acinetobacter also tends to be resistant. Very few adverse responses have been reported.

Clavulanic Acid

This beta lactamase inhibitor has been combined with Amoxicillin and inhibits these enzymes in *H. influenzae*, *E. coli* and *Klebsiella*. It has proven efficacy in the therapy of skin and urinary tract infections with these organisms.

Sulbactam

This drug also is a beta lactamase inhibitor, active against these enzymes in *Enterobacter*, *Citrobacter freundii*, *Providencia* and indole positive *Proteus spp.* as well as *Bacteroides* and *S. aureus*.

The Aminoglycosides

Due to rapid resistance development in gram-negative rods, streptomycin has been replaced by gentamicin, tobramycin, netilmicin and amikacin and streptomycin has been relegated to the therapy of relatively few organisms. These drugs act by inhibiting protein synthesis inter alia. Transport of these agents into bacteria is an energy dependent process. Chloramphenicol blocks this transport and this explains the antagonism between these compounds. Three mechanisms operate in aminoglycoside-resistant organisms, viz reduced transport, enzyme-mediated inactivation and deficient target binding.

These drugs are usually administered parenterally, barring Neomycin (mainly used for oral bowel decontamination) and are widely distributed in body fluids and tissues. CSF penetration, however, is bad. Excretion is renal and high levels are found in the kidneys and urine. Reabsorption takes place in the proximal tubules and this phenomenon is responsible for the associated nephrotoxicity.

A double compartment model describes distribution of these drugs adequately, and therefore peak levels are determined one hour after administration and trough levels just before initiating administration. Half-life is between 90 and 200 minutes. Toxicity is related to the duration of therapy and the area under the drug level curve. Renal toxicity does not occur before 72 hours' administration of the drug. Dosage is therefore adjusted according to serum creatinine levels as well as drug levels. Due to direct chemical inactivation

aminoglycosides and beta lactam antibiotics should not be mixed in infusion fluids, but administered separately.

A loading dose of 1.5 to 2 mg/kg for all aminoglycosides excepting amikacin and kanamycin (7.5-8 mg/kg) is advisable and is not affected by renal function. In patients with normal renal function this dose is then administered eight-hourly. Drug levels are a very useful guide to therapy and should be done initially and weekly after stabilization until therapy is discontinued. Three times a week, creatininium should be determined and levels estimated should creatinine rise. It should, however, be emphasized that on the fifth day of therapy the required dose of aminoglycoside is decreased and adjustment may be necessary. Ototoxicity is related to total duration of therapy and the area under the curve may manifest as high frequency deafness or vestibular toxicity.

Nephrotoxicity is similarly related to drug pharmacokinetics, but the diseased kidney accumulates less aminoglycosides excluding streptomycin. Neuromuscular toxicity may lead to neuromuscular paralysis in patients receiving synaptic blockade.

Aerobic and facultative gram negative bacilli as well as *S. aureus* are sensitive to this group of antibiotics. Streptomycin is used for a limited spectrum of organisms including *Brucella*, *Yersinia pestis* and *M. tuberculosis* and in combination occasionally for *S. faecalis* and *S. viridans*. One gram daily in divided doses is the recommended dosage of this drug in these settings.

Gentamicin has a wide spectrum against gram negative rods, but has the most limited spectrum of the available drugs with good activity against *S. aureus*, some enterococci, *E. coli*, *Klebsiella spp*, *Enterobacter spp*, *Serratia*, *P. mirabilis*, *M. morgagni* and *P. vulgans*. Tobramycin is less active against *S. aureus*, the enterococci, *E. coli*, *Enterobacter* and *Serratia*, while it is considerably more active against *P. aeruginosa*. Amikacin is likewise less active against gram-positive organisms, but it is active against the vast majority of organisms resistant to the other aminoglycosides. Netilmicin is better than gentamicin against *E. coli*, *Klebsiella spp*, *Enterobacter spp*, *Serratia*, *P. mirabilis*, *M. morgagni* and *P. vulgans*. Tobramycin is less active against *S. aureus*, the enterococci, *E. coli*, *Enterobacter* and *Serratia*, while it is considerably more active against the vast majority of organisms resistant to other aminoglycosides. Netilmicin is better than gentamicin against *E. coli*, *Klebsiella*, *Enterobacter* and *Citrobacter*. Spectinomycin differs from other aminoglycosides in the absence of nephro- and ototoxicity and is used only in the therapy of the gonococcus (excluding rectal and pharyngeal disease due to bad penetration).

Drug levels taken during therapy with this category of drugs is more often subtherapeutic than toxic, particularly early on during therapy. A 70 kg person should receive about 120 mg eight hourly of gentamycin, tobramycin or netilmicin.

Chloramphenicol

This is probably one of the most widely applied antibacterial agents in spite of its toxicity. Its mode of action is through inhibition of protein synthesis. At achievable

concentrations it is cidal for *H. influenzae*, *S. pneumoniae* and *N. meningitidis* while it has a static effect on the vast majority of other organisms.

Good absorption is a well-known attribute on oral, as well as intramuscular administration. It is glucuronated in liver and excreted in its inactive form renally. Due to the grey syndrome, chloramphenicol was previously considered contra-indicated in the newborn, but drug level estimation technology has changed this dictum dramatically. The half life is about four hours and it diffuses well into most bodily tissues and fluids including CSF.

Side effects include a dose related, reversible toxic bone marrow suppression and the much more ominous irreversible idiosyncratic bone marrow affliction. A G6PD deficiency mediated haemolytic anaemia occurs, but it is much less common in blacks with a milder deficiency. The grey syndrome consists of vomiting, obstipation, flaccidity, circulatory collapse and death. An optic neuritis, peripheral neuritis, ophthalmoplegia and confusion have all been described. The drug may slow conversion of drugs such as tolbutamide, chlorpropamide, warfarin and metabolism of the drug may be accelerated by phenytoin and phenobarbital.

Although most gram negatives are inhibited by it, it is also active against most anaerobes as well as spirochetes, rickettsiae, chlamydiae, mycoplasmas. It is indicated in the therapy of *Salmonella*, meningitis in childhood (*H. influenzae*, *N. meningitidis* and *S. pneumoniae*).

Resistance to this therapeutic agent is produced by an acetyltransferase that inactivates the antibiotic.

Tetracyclines

After entry by an energy-dependent process, ribosomal binding and protein synthesis inhibition ensues. Minocycline is the most active agent followed by doxycycline and the much less active oxytetracycline and tetracycline. *H. influenzae* and *S. pneumoniae* are inhibited by this drug.

Gonococci sensitive to penicillin and meningococci are susceptible as are community acquired gram negatives such as *E. coli*. *Shigella spp* have become progressively more resistant but *V. cholerae* remains susceptible. Actinomyces is inhibited excellently and anaerobes generally are sensitive. Of the parasites *E. histolytica* and *P. falciparum* are treated with these agents.

Thrombophlebitis is common with parenteral therapy. The longer-acting doxycycline and minocycline are absorbed much better than the other congeners. Although these drugs are distributed widely, insufficient levels exist in the CSF. Crossing the placenta, these drugs should not be used during pregnancy as is the case during lactation and in young children where bone and teeth deposition may occur and stain teeth.

Side effects include nausea, vomiting and epigastric distress. Diarrhoea may be seen due to changes in the bowel flora. Hepatotoxicity is well described as is the precipitation of

renal failure. Reversible vestibular toxicity is a major drawback in the application of this drug to therapy.

Cimetidine decreases levels due to depression of absorption. Carbamazepine, diphenylhydantoin and barbiturates shorten half-life through microsomal liver enzyme induction.

Rifampicin

Rifampicin inhibits the action of DNA dependent RNA-polymerase. The drug is excreted through the liver and penetrates well into CSF.

The drug is active against the *Neisseria spp* and *H. influenzae* as well as staphylococcal species, but resistance arises rapidly in staphylococci. Marked activity exists against *M. tuberculosis* as well as *Legionella spp*. Activity is also found against *Chlamydia*.

The most important side effects is hepatitis, although asymptomatic elevation of enzymes occurs much more commonly. Proteinuria occurs commonly but renal failure is rare. Rashes and gastrointestinal abnormalities occur commonly. An acute flu-like illness may be associated with interstitial nephritis and acute tubular necrosis as well as thrombocytopenia and hemolytic anaemia.

INH increases the probability of toxic hepatitis, and the drug decreases in the half life of drugs including prednisone, ketoconazole, quinidine and digitoxin.

The most common application for this drug is in therapy of mycobacterial diseases, including leprosy. It is also often used for prophylaxis during *N. meningitidis* and *H. influenzae* outbreaks. Enhanced killing of *S. aureus* has been described in combination with vancomycin and fusidic acid, but it should never be prescribed alone for this organism.

Rifampicin has been advocated to eradicate nasal carriage of *S. aureus*, but mupirocin has probably substituted it for this indication.

It also is suggested therapy, in combination with erythromycin, for persistent legionella cases, and it has been used for *Brucella* infections.

Metronidazole

This drug is absorbed excellently after oral and rectal (suppository) administration. Intravenous administration is advised, however, at initiation therapy. Tissue and body fluid penetration is excellent. As excretion is mainly hepatic, dosage adjustment should be considered in patients with hepatic failure.

The drug acts by interaction with DNA and other macromolecules, intermediate compounds or free radicals. It is a potent anti-anaerobic drug but is notable for its lack of activity against *Clostridium spp* other than *C. perfringens* and gram-positive non-sporulating bacilli. Due to rapid reduction by bowel flora, little change in bowel flora occurs.

Trichomonas vaginitis was the initial therapeutic indication and this was rapidly followed by amoebiasis and giardiasis. As an anti-anaerobic drug metronidazole has been very effective except in patients with cerebral abscesses. Although the drug has been utilized in patients with Crohn's disease, this indication remains controversial. It is commonly recommended as a prophylactic agent in cases of colon surgery.

Mutagenicity is an important cause for concern, but this information cannot be extrapolated directly to human subjects. The drug is contra-indicated during pregnancy. A disulfiram type reaction is a well-described side effect and alcohol should not be ingested during metronidazole therapy. Seizures, cerebral and cerebellar dysfunction, peripheral neuropathy and pseudomembranous colitis have all been attributed to the drug.

Erythromycin

By binding to the 50S ribosome erythromycin prevents protein strain elongation by transpeptid inhibition. This drug is active against *S. pyogenes* and *S. pneumoniae*. Although *S. aureus* is usually sensitive, resistance has arisen on therapy. Most viridans streptococci are sensitive, as are *Nocardia asteroides* and *Actinomyces spp.* Activity against *H. influenzae*, *B. pertussis*, *Campylobacter* and some gram-negative anaerobes (not *B. fragilis*) exists. *Mycoplasma* and *Ureaplasma* are sensitive, as is *T. pallidum* and *Legionella*.

Absorption may differ considerably between preparations after oral administration. Side effects include epigastric discomfort, nausea and vomiting. Allergic skin rashes and fever occasionally occur. Superinfection and pseudomembranous colitis are obvious side effects. A cholestatic hepatitis with an eosinophilia may occur with estolate in adults. Reversible hepatotoxicity occurs with the ethylsuccinate and possibly other erythromycin preparations. Many drugs are incompatible with erythromycin in IV infusion fluids. Theophyllin blood levels and toxicity are increased by this antibiotic. Erythromycin is the drug of choice for *M. pneumoniae*, *Legionella*, *Chlamydiae* and *Campylobacter* infections. Furthermore it is a useful alternative in the therapy of streptococcal infections (including *S. pneumoniae*) and may be used for rheumatic fever prophylaxis, non-gonococcal urethritis, primary and secondary syphilis and pulmonary anaerobic infections. Dosage for adults ranges from one to four grams daily.

Clindamycin and Lincomycin

These drugs inhibit protein synthesis via ribosome binding. Clindamycin is produced by chemical modification of lincomycin. It is active against staphylococci, *S. pyogenes*, viridans streptococci and *S. pneumoniae*, but is inactive against the enterococci and gram-negative anaerobes. Anaerobically, it is notable for its activity against *B. fragilis*, while approximately 15% of clostridia are resistant to the antibiotic. *S. aureus* may become resistant to this drug during therapy.

Absorption after oral administration is good and penetration to all tissues and fluids excluding CSF is good. It has a serum half-life of about 140 minutes and is metabolized by the liver.

Doubling of serum half-life occurs during severe renal failure and dosage is halved in these cases. Allergy may occur although anaphylaxis is rare. Hepatotoxicity is rare, as is neutropenia and thrombocytopenia. Diarrhoea occurs in about a quarter of all patients and may be due to *C. difficile* (pseudomembranous colitis), but this certainly occurs with virtually all other antibiotics.

This drug has been widely used for lung, intra-abdominal and gynaecologic anaerobic infections and has been used successfully in cases of osteomyelitis due to *S. aureus*.

Vancomycin

This drug inhibits cell wall composition and alters cytoplasmic permeability. Administration should never be at a rate faster than 500 mg in 30 minutes due to the development of histamine mediated flushing in the head and neck area. The drug is eliminated renally and total renal failure leads to accumulation with a half life increase from six hours to seven days (total renal failure). Adequate body fluid and tissue concentrations are attained, although the drug does not cross the blood brain barrier into CSF.

Phlebitis is commonly experienced, but the most problematic side effect is tingling and flushing (red-neck syndrome) as described above. Rashes are rare. Ototoxicity is the major toxic effect due to nerve damage. Nephrotoxicity is rare in single-agent therapy, but common on combination with aminoglycosides.

Notable antibacterial activity exists against *S. aureus*, *S. epidermidis*, *S. pyogenes*, group B streptococci, *S. pneumoniae*, the JK bacillus and *S. faecalis* is often sensitive, but combination with an aminoglycoside in therapy may be advisable, i.e. in therapy of endocarditis.

In patients with normal renal function 2 g IV per day (30 mg/kg) in 2 to 4 divided doses is the usual dose. In renal failure dosage adjustment is essential to prevent toxicity. Oral therapy with 125 mg six-hourly is adequate for pseudomembranous colitis. Gentamicin, rimpicin or cotrimoxazole may be added in combination for *S. aureus* infections. Intrathecal administration may be necessary for meningitis in certain categories of patients.

In penicillin-allergic patients this drug may be used as prophylaxis as a single one-gram dose.

Antifolate Agents

The Sulphonamides

Sulphonamides are structurally similar to PABA (necessary for folate synthesis) and therefore interfere with folate synthesis with subsequent depletion of folic acid due to inhibited synthesis. This group of drugs is active against *S. aureus*, including many methicillin resistant strains, *S. pneumoniae*, *S. pyogenes*, *E. coli* (up to 40% resistant), *Klebsiella*, *Proteus mirabilis*, *Shigella spp*, *H. influenzae*, *Chlamydia*, *Nocardia* and *Actinomyces*. Of the parasites, *Plasmodium*, *Toxoplasma* and *Pneumocystis* are susceptible.

Resistance occurs due to PABA overproduction or enzyme modification to decrease completion with PABA.

Sulfisoxazole, sulfamethoxazole, sulfadiazine, sulfamethisole, and sulfadimidine are all short-acting substances whereas sulfadimethoxine and sulfadoxine are long-acting agents. Sulfadoxine is contained in Fansidar while sulfamethoxazole is to be found in co-trimoxazole combinations. Sulfaguanidine, sulfasuxidine and sulfathidine are badly absorbed after oral administration. Salicylazosulapyridine, by contrast, is used for inflammatory bowel disease. Mafenide acetate and silver sulfadiazine are used as topical agents. The activity of the latter is based on slow release of the silver and is used for burns.

Generally these agents are administered orally. Parenteral administration is necessary, however, in the therapy of *Pneumocystis carinii* infections, and occasionally for staphylococcal disease. These drugs are absorbed well after oral administration and distributed to all body fluids and tissues, with the exception of the agents set aside for gastro-intestinal application. Conjugation occurs as the most important elimination process. Renal excretion is important in elimination of these drugs, and they accumulate in renal failure.

Side effects may include gastro-intestinal (nausea, vomiting and diarrhoea) and renal crystaluria (pushing fluids is advisable as is urinary alkalinization). Due to competition with albumin binding sites, this drug should not be used in neonates or pregnant women as it may accentuate kernicterus. A hemolytic anaemia may occur in G6PD deficient subjects. Drug eruptions, erythema multiform and Stevens Johnson syndrome, vasculitis and anaphylaxis have been described. Due to drug displacement, warfarin and methotrexate toxicity may be elicited.

Urinary tract infections, *Nocardia asteroides*, toxoplasmosis, malaria, LGV, trachoma and other chlamydial infections have been treated with this drug.

Trimethoprim

This drug acts by inhibiting dihydrofolate reductase and acts synergistically with the sulfonamides in the folic acid pathway of bacteria. Due to lacking synthetic capability of human tissue to synthesize folic acid, human folate utilization may be impaired by trimethoprim. The drug is available as a single agent or in combination with sulfamethoxazole in a 1:5 ratio (20% trimethoprim). The drug is distributed widely in body tissues and fluids and is excreted renally unchanged or as inactive metabolites. Biliary excretion accounts for the rest. Dosage is halved in patients with a creatinine clearance of 15 to 30 mL/min and not recommended in patients with more severe renal deficiency.

Side effects include megaloblastosis and folate decreases the effect during therapy. Renal function may be compromised.

Trimethoprim has a wide spectrum of activity against most gram positives including *S. faecalis*, but not *Clostridium spp.* The gram-negative spectrum includes most *Enterobacteriaceae*, but the effect is less. It is too inactive against *Serratia*, *Pseudomonas spp* and *Nocardia*. Synergism applies with sulfamethoxazole against most gram-negative

organisms, but many *Serratia* and *Pseudomonas spp* remain resistant, although *Nocardia* becomes highly sensitive.

Trimethoprim has been used effectively for urinary tract infection, as has the combination. The combination has been used effectively for pneumonia and is an accepted alternative therapy for sinusitis or otitis media. *Shigella*, *Salmonella* and *E. coli* diarrhoeal disease is treated effectively with the combination. The combination is also used successfully against *Brucella*, *Nocardia* and *Toxoplasmosis*.

Quinolones

Nalidixic acid is the oldest of these compounds and is notorious for the amount of resistance generated. Cinoxacin, oxolonic acid, ploxacin, ofloxacin and ciprofloxacin were all developed later on. All of these chemically related compounds act by inhibiting DNA gyrase and so doing supercoiling of bacterial DNA. As this action is reversible, the exact cidal mechanism has not been described yet.

Gram-positive activity in vivo is poor, even when in vitro sensitivity can be demonstrated. These agents are active against the vast majority of *E. coli*, *Proteus spp* including *P. mirabilis*, *Enterobacter* and *Klebsiella*. *Pseudomonas* is resistant to nalidixic acid. Cinoxacin and oxolonic acid are more active than oxolonic acid and more reliably includes organisms such as *Salmonella*, *Shigella*, *Acinetobacter* and *Haemophilus*.

Norloxacin and ciprofloxacin are considerably more active (up to a hundredfold or more) and these agents make oral therapy of highly resistant gram negatives possible. MICs for most gram negatives are below 1 mg/mL excluding *Providencia*, some *Proteus spp* and *Acinetobacter* in the case of norfloxacin. Most of these organisms are, however, sensitive to ciprofloxacin, of which the spectrum also includes many gram positives, but clinical results remain disappointing against gram positives.

Absorption after oral administration is excellent. The compounds are partially metabolized in the liver and excreted renally (85% conjugated). The older agents have a half-life of approximately one hour, while that of norfloxacin is seven hours, and ciprofloxacin four hours.

Nausea, vomiting, diarrhoea and abdominal pain occur rather frequently, while skin rashes, pruritus, urticaria and sun sensitization are somewhat rarer complications. Eye changes include diplopia and changed colour perception. Central nervous system side effects include vestibular and sensory symptoms, grand mal seizures and pseudotumour cerebri. Due to the possibility of haemolytic anaemia, the drug should be avoided in patient with G6PD deficiency. Caution is advised in patients with hepatic failure.

Nitrofurantoin

Nitrofurantoin is a urinary tract antibacterial active against *E. coli* and other coliforms. *Klebsiella* and *Enterobacter* are somewhat less susceptible while *Proteus* and *P. aeruginosa* is resistant.

The drug is rapidly absorbed after oral ingestion, but low serum and body fluid concentrations (excluding kidney tissue and urine) are attained. The half life of 20 minutes increases dramatically in patients with renal failure (a contra-indication of its use). A large proportion of the drug is metabolized rapidly. Alkaline urine decreases the activity of the drug. Anorexia, nausea and vomiting occur frequently. Allergic lung, liver, blood and skin manifestations occur as does drug-induced lupus erythematosus. A variety of allergic skin rashes may occur. Steroids are useful in these cases (most notably for pulmonary disease). The liver may be affected by hepatocellular or cholestatic processes and many neurological complications have been described including a peripheral neuritis that may progress, should therapy not be discontinued immediately.

This drug is used mainly as a urinary antibacterial agent.

Methenamine

This urinary antiseptic is toxic to bacteria due to hydrolysis to ammonia and formaldehyde and proper acidification of urine is essential. Combination with mandelic or hippuric acids is commonly practised to render the urine acidic, but very large doses of these acids are necessary to secure effectivity. Normal urine is, however, most often adequately acid to hydrolyze the drug.

Methenamine is widely active via its metabolites against gram positive, gram negative and fungal etiologic agents, although *Proteus sp* may destroy the active compound.

Absorption is rapid, but the drug is contraindicated in hepatic failure due to ammonia production and it is rapidly excreted in urine.

Antifungal

Nystatin

This topical and oral antifungal is potentially toxic, but not absorbed. Subcutaneous infection does not respond to therapy. 100000 unit pessaries are applied daily for 14 days, but a high failure figure rate occurs for vaginal candidiasis. A suspension of 100000 units/mL is swirled through the mouth and swallowed for oral candidiasis. Large doses may be used to sterilize the gastro-intestinal tract, but has no advantage via this route for vaginal candidiasis.

Amphotericin B

This antibiotic is the standard by which all antifungal agents are measured. The drug is degraded metabolically and does not accumulate during renal or hepatic failure and dosage adjustments is therefore unnecessary in such patients. Tissue and body-fluid penetration generally can be considered reasonable excluding CSF and vitreous humour, even when these sites are inflamed.

Toxicity is largely renal with an early, pronounced potassium leak. It is essential that this electrolyte must be replenished under these conditions. A test dose of 1 mg is generally given over 10 to 20 minutes. Reactions may dictate addition of cortisone on subsequent

administration. In patients already being treated with steroids, no additional benefit accrues from additional steroid therapy. The dose is thereafter slowly advanced to 0.6 to 0.7 and (seldom) 1 mg/kg/day. Infusions are administered over two to six hours. Dosage reductions is sometimes advocated to keep the creatinine below 400 mEq/L. In cases where more rapid escalation of dosage is considered necessary, 0.1 mg/kg/day may be administered as a test dose over four to six hours, followed immediately by a further 0.3 mg/kg/day and advanced to the final dose over the next two days.

Other side effects include thrombocytopenia and neutropenia. Amphotericin is the drug of choice for *Candida*, *Cryptococcus*, *Aspergillus* and mucormycoses. By contrast to most systemic infections, esophagitis is treated with a low dose of the drug (10 mg daily for seven to 10 days). Although the drug is also effective against *Histoplasma* and *Blastomyces*, it is not the drug of choice. Combination with 5 fluoro cytosine is advocated in the therapy of *Cryptococcus* and sensitive *Candida* species. Although in vitro synergism with rifampicin is much more promising, advantage in animal models has only been demonstrated for *Histoplasma*, *Blastomyces* and *Aspergillus*. Combination with ketokonazole is not advised at present.

5 Fluoro Cytosine

Virtually all the administered drugs is excreted renally necessitating dosage reduction in patients with renal failure. Gastro-intestinal absorption is complete and CSF penetration is excellent. With normal renal function the half-life is two and a half to five hours. The drug acts by interfering with thymidine synthesis. In patients with normal renal function 37.5 mg/kg is administered six-hourly. Drug levels are most helpful in the prevention of toxicity. Gastro-intestinal side effects are commonly found, but bone marrow toxicity is potentially the most serious complication. Combination with amphotericin B is necessary when the drug is used for *Candida* and *Cryptococcus* due to the development of resistance on single agent therapy with the drug. The dosage of amphotericin B can be reduced and nephrotoxicity limited by combination therapy.

The Imidazole Group of Drugs

Ketoconazole and a number of topical agents are presently available. Itraconazole (at present an experimental drug) holds much promise for the future. As with amphotericin B, these drugs interfere with membrane sterol synthesis. It is highly active against most pathogenic fungi including aspergillus.

Ketoconazole

Ketoconazole is inactivated by the liver and excreted mainly in bile. Renal and hepatic disease do not affect drug levels. A terminal half-life of about 10 hours has been demonstrated. Normal gastric acidity is crucial to obtain satisfactory blood levels. It is often effective in therapy of *Blastomyces*, *Histoplasma*, and mucocutaneous but not systemic *Candida* infections. Nausea, vomiting and alterations of steroid synthesis are the most common side-effects. Clotrimazole, miconazole and econazole are used mainly as topical antifungal agents.

Antiviral Agents

Acyclovir

Acyclovir is active against HSV 1, HSV 2, VZV and EBV, while much higher concentrations are necessary to inactivate CMV. The drug acts by inhibiting viral DNA synthesis by active competition for thymidine kinase. Viruses of the abovementioned classes become resistant to the drug by changes in the thymidine kinase enzyme.

The drug is excreted renally, largely unmetabolized. A plasma half-life of approximately three hours is found and approximately a quarter of the drug is absorbed on oral administration and distributed widely in body fluids (CSF penetration amounting to roughly half plasma levels).

A small number of patients experience encephalopathic side effects. The most serious side effect is bone marrow depression, that generally is reversible.

Topical application has been found to be satisfactory for genital lesions, but does not decrease the incidence of relapses, as is the case with oral administration. The oral preparation is used in therapy of genital herpes and in higher dosage for herpes zoster (the drug is half as active against this virus as against herpes simplex). Disseminated herpes simplex is effectively treated by 15 mg/kg/day while 30 mg/kg/day is necessary for herpes encephalitis, pulmonary chickenpox and disseminated zoster.

Other Antiviral Agents

Amantadine has an anti-influenza virus effect, while bromovinyl and deoxyuridine is active against herpes viruses. Vidarabine has been rendered virtually obsolete by acyclovir. Dihydroxyproprymethylguanidine is potentially most useful in the therapy of CMV infections.

Antibiotic Prophylaxis

In surgery, prophylaxis constitutes a major portion of antibiotic use. The following general principles are applicable under these circumstances:

- Administration should be aimed at obtaining peak tissue levels at or shortly after surgical incision. The value of administered antibiotics declines rapidly, being of no value when administered more than six hours after incision.

- Brief administration, limiting exposure to a period of 24 hours or less but never more than 72 hours, is important, as the incidence of infection on prolonged (more than 72 hours) prophylaxis increases.

- The spectrum of activity of the antibiotic should be restricted to the utmost and therefore the choice is directed by the pathogens expected according to the site of operation, the hazard for infection, and statistically proven benefit for prophylactic antibiotic use.

- The risk for infection is determined largely by the type of operation, i.e.:

- clean, uncontaminated surgery which is defined as glabrous skin incision made under controlled clean conditions not entering a hollow organ: prophylaxis is indicated only when the type of ensuing infection is catastrophic as occurs during prosthetic cardiac, vascular and orthopaedic operations.

- clean, contaminated surgery which is defined as controlled incision of a hollow organ other than colon, when the site of operation is not infected: prophylaxis is limited to endocarditis prophylaxis, i.e. tooth extraction in patients with prolapsing mitral valve disease

- contaminated surgery exists when controlled incision of the colon is performed and is an indication for prophylaxis

- dirty or infected surgical procedures warrant prophylactic or therapeutic administration of antibiotics

- the efficiency of prophylaxis should be monitored on an ongoing basis in a particular hospital

- effective, high dose prophylactic regimens should be instituted

- cost should be contained as far as possible within the dictates of good patient care, using minimal dosage periods.

Prophylaxis for Specific Surgical Procedures

Clean Uncontaminated Surgery

This can be defined as surgically controlled skin incision without accompanying incision of a hollow organ. Generally no prophylaxis is indicated excepting when transplant surgery or placements of prosthetics is undertaken. The most frequent organisms involved in infections are *S. aureus*, *S. epidermidis*, diphtheroids and a few gram negative aerobic rods. Under these circumstances the drug of choice is a first-generation cephalosporin in full doses for 24 hours, i.e. cefazolin 1 g eight-hourly for three doses.

Clean Contaminated Surgery

Incision of a hollow organ such as the mouth, pharynx or oesophagus is termed clean and uncontaminated. For these surgical procedures (including mouth surgery and dental procedures), prophylaxis is only indicated in those at risk for infective endocarditis. (Congenital, rheumatic, prosthetic and mitral valve prolapse patients.) The prophylactic regimen of choice is penicillin G 1 million units plus procaine penicillin G 600000 units one hour before operation followed by pen VK 500 mg six-hourly for eight doses. In patients with heart valve prostheses gentamicin 1.5 mg/kg should be added to prevent gram negative endocarditis. In penicillin allergic subjects vancomycin 1 gm is administered one hour before

operation and followed up with erythromycin 250 mg six-hourly. A loading dose of penicillin VK (2 gm) followed by pen VK as above is also acceptable.

Endocarditis prophylaxis for gastro-intestinal or genito-urinary manipulations consists of crystalline penicillin G 1 million units or ampicillin 1 g, either of which is combined with gentamicin 1.5 mg/kg administered intramuscularly or intravenously (two doses of each).

In allergic patients vancomycin 1 gm is administered intravenously. When oncologic surgery is performed in the head and neck region and a breach of mucous membrane occurs, penicillin G (1 million units) or ceftazidime (1 g) may be used prophylactically, as the most important pathogens are *S. aureus*, coliforms and oral anaerobes.

For caesarian section and vaginal hysterectomy ceftazidime 1 gm before and six-hourly for three doses or ceftiofuran 2 gm administered at similar interval, with the same duration as for ceftazidime. Although these antibiotics are not active against the enterococcus, they are active against the majority of other potential pathogens. Generally infection after these procedures is caused by *S. epidermidis* enterococcus, non-enterococcal group D streptococci, coliforms, *Peptostreptococcus* and *Bacteroides sp.* These infections are usually mixed, should they occur, but therapy of some portion of such a mixed infection generally causes the demise of the other organisms involved.

Biliary surgery is also considered clean contaminated, but prophylaxis is considered necessary after the age of 70 years, when organisms are seen on gram stain, cholecystitis within the preceding two weeks and in patients with diabetes mellitus (*Clostridium sp* are important). Ceftazidime 1 gm eight-hourly (three doses) plus penicillin G 2 million units six-hourly (four doses) or ceftiofuran 2 gm six-hourly (four doses) is administered (Ceftiofuran has sufficient anti-clostridial efficacy).

Peptic ulcer surgery warrants prophylaxis only in high risk cases, i.e. achlorhydria, stomach outlet obstruction, haemorrhage, but not in cases with perforation. The mouth anaerobes, aerobic gram positives and a few gram negative enterobacteria are involved in infection. Ceftazidime 1 gm eight-hourly is the drug of choice.

Contaminated Surgery

In appendicitis and cold colonic surgery, the most common expected pathogens are the enterococci, *Enterobacteriaceae* and anaerobes. Suggested prophylaxis under such circumstances includes gentamicin 1.7 mg eight-hourly (three doses) and clindamycin 600 mg six hourly (four doses) or gentamicin plus metronidazole 500 mg eight-hourly IVI. Alternatively four six-hourly administrations of ceftiofuran suffices (2 gram doses).

In open fractures adequate debridement is essential, but prophylaxis with a first-generation cephalosporin has been proved beneficial.

Dogs and human bites should receive penicillin G 1 million units six-hourly (four doses), gentamicin 80 mg eight-hourly and metronidazole 400 mg eight-hourly for five to seven days.

Dirty or Infected Wounds

These conditions necessitate therapeutic antibiotic intervention.

Comment

Antimicrobial Agents and Infection

H O Penzhorn

The chapter on different antibiotics gives a good overview over the available drugs with their spectrum of activity and complications.

The first-generation cephalosporins is indicated mostly for community-acquired cellulitis. They have no specific advantage over non-cephalosporin agents, but are relatively safe and competitively priced. In mixed infections which involve anaerobes, particularly *B. gracilis*, against whom they are ineffective, they can be combined with any other agent, usually an aminoglycoside or an extended spectrum penicillin as empirical therapy for sepsis of unknown aetiology. The classical combination being cephalothin with gentamycin sulphate which is just as effective as any other single agent in this situation.

The second-generation cephalosporins are active against selected groups of aerobic and anaerobic rods, but non-effective against pseudomonas and enterococci. They can be divided into two groups. The first group (cefamandole, cefuroxime) is "enterobacter-active" with activity against *H. influenzae* and enterobacter. The second group (cefoxitine) is "*B. fragilis*-active" with activity against *B. fragilis* and 25-50% of *Serratia spp.*

As a group they are not active against most multiply of drug-resistant hospital-acquired pathogens and they cannot be used alone in hospital-acquired infections. Cefoxitine is effective against community-acquired *B. fragilis* infections (diverticulitis and faecal soiling of the peritoneum) and active against *S. aureus* and coliforms. It can thus be used as a single agent in most instances of mild to moderate intra-abdominal infections. It is not the best drug available for *B. fragilis*, and clindamycin-HCl or metronidazole will companion drugs such as cefuroxime are preferable for overt sepsis from anaerobic bacteria.

The third-generation cephalosporins are less effective against staphylococci and streptococci with variable anaerobic activity (especially against *B. fragilis*). They have variable activity against pseudomonas (so-called "anti-pseudomonal cephalosporins") but in the therapy of this organism, combined therapy is advised by many authors. Their specific advantage is that in serious defined infections and serious infections of unknown origin, they are often the least toxic of the effective agents. Unlike the second-generation cephalosporins, the third-generation cephalosporins are fairly similar in their antibacterial spectrum. Cefotaxime and ceftriaxone have practically the same spectrum which is very good against gram-positives (staphylococci) and fair activity against *B. fragilis*. In anaerobic intra-abdominal or pelvic infections they should probably be combined with an agent that is effective against anaerobes. Their activity against pseudomonas is only fair and more specific drugs like piperacillin sodium should be used instead. Moxalactam and ceftazidime are

somewhat different from other third-generation cephalosporins. Moxalactam is not active against gram-positives and the most effective of the third-generation cephalosporins against anaerobic infections, like cefoxitine of the second-generation cephalosporins, ceftazidime, has relatively poor activity against anaerobes, but is very good against pseudomonas. It can be used against the latter, particularly in conjunction with aminoglycosides.

Antimicrobial prophylaxis in surgery had a great effect in the evolution of modern surgery. It has become clear that antimicrobial need not be given before the induction of anaesthesia, as unexpected delays in surgery may lead to a fall in serum concentrations before effective levels. In prolonged procedures repeated administration of antimicrobials may be crucial. A brief course of antibiotics is capable of sterilizing tissues, only if it is administered at the time of inoculation. The division of the surgical procedures in four broad groups have marginal usefulness because of our current level of understanding of infection. Within the clean surgery category, for example, infection rates may vary considerably. Although the list of pathogens known to cause a postsurgical wound infection is extensive, most infections are due to a limited number of pathogens with limited resistance to antimicrobial agents. The infecting organisms for given surgical procedures are well defined and microbial activity broad enough to cover all potential pathogens is not required. Hospitals must, however, maintain an up-to-date analysis of the antimicrobial susceptibilities of surgical wound isolates to detect important shifts in patterns of resistance. The most likely infecting organisms are not predictably correlated with the most prevalent contaminating organism. For instance, in gynaecologic surgery, the anaerobes which represent a major segment of the colonizing genitourinary tract flora are rarely encountered as pathogens in elective obstetrical-gynaecologic surgery. Prophylaxis with antimicrobials effective against anaerobic gram-negative rods is usually efficient. Thus the most likely pathogens must be determined empirically. Because of their antimicrobial spectrum and relative lack of toxicity, the cephalosporins are the agents of choice for surgical procedures in which skin flora (staphylococci) and normal flora of the gastro-intestinal and urinary tracts are the most likely pathogens.

In clean and clean-contaminated surgical procedures in which the most likely pathogens are usually susceptible to first-generation cephalosporins, second or third-generation cephalosporins provide no better prophylaxis than cefazolin. Because of failure to maintain adequate serum and tissue levels throughout surgical procedures, the shorter acting cephalosporins have been associated with increased infection rates. Within the hospital environment, there are theoretical disadvantages to the routine use of antibiotics with the broader spectrum of antimicrobial activity. There are subtle differences in the *in vitro* effectiveness of various cephalosporins against common bacterial pathogens, particularly the staphylococci. These differences may be important clinically, and therefore one should not assume that the various cephalosporins can be used interchangeably in surgical wound prophylaxis. The choice of specific cephalosporins should be based on the results of adequately executed clinical trials. Cefoxitine has been recommended for use in appendisectomies and colorectal surgery, in which anaerobes are important pathogens. The emergence of resistant bacteria is not a problem if prophylaxis is given for only 48 hours. After four day prophylaxis resistance may emerge. It can be concluded that the reduction in morbidity and mortality resulting from rational employment of prophylactic antibiotics has clearly been demonstrated.

Chapter 1.5: Nuclear Medicine Procedures in Surgical Diagnosis

M P Iturraide

Introduction

As with other imaging modalities, i.e. CT, NMR, x-rays, US, the great value of nuclear technology lies in its capability for non-destructive measurements, but there are important differences. Where the former provide information primarily about the body structures, radioactive tracers make measurements of regional function possible. As such, nuclear medicine brings together structure and function, which in biological systems can be thought of as two aspects of a unitary process. This fact is of capital importance, as there is an increasing realization that the identification of human disease depends significantly on early characterization of local organ dysfunction, rather than on the detection of destroyed tissue structures alone.

General Principles

Nuclear medicine imaging combines the administration and detection of the gamma-ray emissions from radiopharmaceutical agents having specific distribution in the body and the *in vivo* reconstruction of the radiotracer tissue concentrations.

Radiopharmaceuticals

Most of the imaging techniques described in this chapter use a radionuclide linked to a suitable chemical (radiopharmaceutical) to study the particular tissue, organ, or area of interest. In scintigraphy radiopharmaceuticals are used in trace amounts and do not have pharmacologic or toxic actions. Radiation from the diagnostic use of radioisotopes is minimal, and no radiation effects have been reported.

An ideal radiopharmaceutical is one which is safe both to handle and administer to patients, fit for the purpose for which it is intended, and readily available at a reasonable cost. In choosing a radiopharmaceutical, consideration must be given to the physical properties of the radionuclide, the chemical and biological properties of the radiopharmaceutical, including *in vivo* and *in vitro* stability, and the ease of preparation of patient doses.

The two most important characteristics of a radioisotope are the nature of the emissions and the physical half-life of the incorporated radionuclide.

Organs and body systems may concentrate selectively on a radiopharmaceutical, eliminate it by means of a specific metabolic pathway, or otherwise deal with it, depending on its chemical and physical constitution. Thus, some substances (notably iodine) go to the thyroid, colloids are taken up by the reticuloendothelial system, phosphate compounds are concentrated in the skeleton, etc. With appropriate radiation detectors (scanners, gamma cameras, whole-body imagers) an image or scan of the *in vivo* distribution of the administered radiopharmaceutical can be recorded.

Pathology can be recognized with these radiopharmaceuticals by:

- Detecting areas of increased concentration of the radiopharmaceutical within an area of relative homogeneous distribution of the radioactive tracer (hot-spot imaging as seen in brain tumours, bone metastases, myocardial infarction)
- Detecting areas of reduced concentration of the radioactive tracer within a uniform radioactive organ (cold-spot imaging as in liver tumours or secondaries, renal or thyroid cysts)
- Monitoring the arrival and disappearance of the radiopharmaceutical over an area of interest (time-activity curves over the kidneys as in renography; the brain as in cerebral perfusion studies; or the heart as in left ventricular volume curves)

Technetium 99m (^{99m}Tc) is the most widely used radioactive tracer employed in *in vivo* investigations. Tc-99m agents have progressed from the application of crude, largely uncharacterized chemistry to probe the functional level of organs such as the lungs, liver, and kidneys to the development of ^{99m}Tc radiopharmaceutical based on a solid structural chemistry foundation.

Advances have also been made for radiopharmaceuticals based on positron and radiohalogen radionuclides. These include radiopharmaceuticals for the heart, brain, and adrenal glands. Exciting results have been obtained with radiolabelled compounds of high specific activity that bind to tissue receptors and the feasibility of imaging receptors in the brain has been demonstrated.

The ability to image a tumour using radiolabelled monoclonal antibody products has been widely demonstrated. Immunoscintigraphy is steadily asserting itself as a valuable method in the localization of malignant tumours, inflammatory lesions and damaged myocardium. In the case of tumours, a monoclonal antibody specific to one or several tumour-cell lines is used. The antibody is labelled with a gamma-emitting radioisotope so that it can be detected *in vivo*, by means of a planar or tomographic gamma camera. It is thus possible to follow daily the distribution of labelled antibodies throughout the body.

Instruments

The Anger scintillation gamma camera is the instrument of choice for imaging both static and dynamic radioisotope distributions *in vivo*. It has been perfected over the years and has been adapted particularly for imaging the 140 KeV gamma rays emitted by Tc-99m.

When gamma rays emitted by a radioisotope strike the collimator front on the head of a scintillation camera, they are projected onto the thin thallium-activated sodium iodide (NaI-Tl) scintillation crystal. The light emitted in the crystal travels in all directions and is detected by an array of photomultipliers which converts the light distribution into a set of electronic signals. The summing network combines these signals into X and Y position signals by finding the centroid of the light distribution. These signals are then normalized in the radio circuit which divides them by the energy signal, Z. In addition, a single-channel analyser selects those events which fall into the energy range corresponding to the gamma-ray energy of the injected radiopharmaceutical. Finally, the normalized position signals are used to form

an analogue or digitized image of the radioisotope distribution in an image readout device which may consist of either a cathode ray tube (CRT) and film or a digital memory and display. This last feature permits recall of the image, application of desired processing, and various forms of temporary and permanent storage.

Mobile gamma cameras with computerized process systems are now used in the intensive care unit or other remote location to perform a nuclear imaging procedure on a patient who has been determined to be too ill to be moved to the nuclear medicine laboratory.

In addition, single-photon emission computed tomography (SPECT) with rotating camera systems is rapidly gaining in popularity, thus extending the usefulness of scintillation cameras. SPECT is an alternative approach to non-invasive medical imaging methodology, its essential goals being the enhancement of the image detectability and the extraction of quantitative data from a true three-dimensional scintigram.

Still another physiologic tomography system is positron emission tomography (PET). This radionuclide imaging modality was immediately perceived as a potentially powerful diagnostic technique and basic tool to study *in vivo*, metabolism and physiology in man. There were two primary reasons for this perception. First, the only gamma-ray emitting isotopes of carbon, nitrogen and oxygen are positron emitters. Therefore, a device capable of imaging positron emitters, would potentially allow *in vivo* study of almost any physiologic or metabolic substrate, since essentially all such substances contain one or more of these elements. Secondly, the physical properties of PET allow one to quantitatively measure the three-dimensional distribution of a positron emitter in the human body. In this way one can mimic the techniques of auto-radiography in man without having to section the body.

Imaging Procedures

Diagnostic nuclear-medicine imaging procedures usually involve the intravenous injection of a radiolabelled agent and the collection of static images of areas of the body in multiple views at some fixed time or times after the injection. Some studies, such as gastrointestinal examinations, require oral ingestion of a radioactive meal, and some, such as ventilation studies, require the inhalation of radionuclide as a gas or aerosol. Dynamic studies usually involve an intravenous injection of a radiopharmaceutical and the collection of multiple images obtained at various time intervals. These images can be further digitized for quantitative data processing, display, and storage in a computer system. In some studies, physiologic and pharmacologic interventions may be used before, during, or after administration of the radiopharmaceutical, to achieve or to enhance the differential distribution of radioactivity necessary to obtain the desired information.

Cardiovascular Scintigraphy

Myocardial Perfusion

Metabolism, Distribution and Pathophysiology

After IV administration, Thallium-201 is rapidly cleared from the circulation. Delivery of thallium to the myocardial tissue is directly dependent on regional blood flow. Thallium-

201 imaging provides definition of the location and extent of the infarcted myocardium and permits distinction between reversible ischaemia and irreversible infarction.

Findings on Perfusion Studies

Acute myocardial infarction: A persistent defect in the initial and delayed thallium images represents an area of scar or infarction.

Ischaemic Heart Disease

Defects present on the initial thallium study, which subsequently resolve on delayed images 2-4 hours later, represent zones of ischaemic but viable myocardium.

Myocardial Infarction Imaging

Metabolism, Distribution and Pathophysiology

Tc-99m phosphate tracer accumulates in regions of myocardial necrosis. Uptake of Tc-99m pyrophosphate by calcium deposits in the infarcted regions demonstrates the location and approximate size of the infarct.

Findings on Pyrophosphate Studies

Acute myocardial infarction: A localized area of the myocardium with increased tracer uptake is characteristic of an acute transmural myocardial infarction and reflects the size and location of the necrotic myocardium.

Cardiac Blood-Pool Imaging

Metabolism, Distribution and Pathophysiology

First-Pass Studies

To accomplish a first-pass study, a radionuclide such as ^{99m}Tc is rapidly injected intravenously and followed closely by a saline flush that propels the bolus forward. Imaging begins immediately. The concentrated bolus allows separate visualisation of individual heart chambers that can be observed successively, as the bolus passes through the cardiovascular system.

Multigated Studies

Gated studies are performed by injecting the patient with ^{99m}Tc after a previous priming dose of "cold" stannous pyrophosphate and by waiting until the isotope reaches a state of equilibrium in the blood pool. Using the R wave of the electrocardiograph to supply triggering signals to the camera, a series of sequential images (frames) of the heart cycle is obtained.

Multigated studies are especially useful in evaluating wall motion and regional ejection fraction, as well as ventricular volume, rate of blood ejection and filling, and cardiac output.

Findings on Qualitative Radionuclide Angiography

Ejection Fraction and Ventricular Volumes

Ejection fraction is an index that can be used for early diagnosis of cardiac pump failure, for prognosis in patients with acute myocardial infarction, for decision-making concerning cardiac operation, for estimating cardiotoxicity from chemotherapeutic agents, for evaluating the effects of cardiac medication, and for assessing cardiomyopathy.

Primarily, right ventricular involvement in chronic obstructive pulmonary disease produces characteristic findings of right ventricle dilation, a reduced right ventricular ejection fraction, and normal left ventricular size and function.

Regional Wall Motion

This method permits evaluation of regional contraction patterns. It is possible to evaluate regional motion visually or by dividing the left ventricle into segments and calculating regional ejection fraction values for each of these areas.

Regions of damaged myocardium secondary to coronary artery disease may result in focal areas of hypokinesis, dyskinesis, or akinesis. Phase analysis of left ventricular wall motion can easily identify paradox motion of aneurysms.

Intracardiac Shunts

Right to left shunts are detected by the early arrival of a tracer in the left side of the heart and aorta prior to or simultaneously with the appearance of a tracer in the lungs by the first-pass method.

Left to right shunts may be identified by the reappearance of tracer activity within the pulmonary vasculature. This results in prolonged pulmonary tracer activity and decreased activity in the left side of the heart and aorta.

Pulmonary Scintigraphy

Perfusion Imaging

Ninety percent of the radionuclide, Technetium macroaggregate albumin (Tc-99m MAA), is trapped in the pulmonary capillaries on the first pass in through the lungs, because the average diameter of a human lung capillary is approximately 7 microns, while the iv injected Tc-99m MAA particles have an average diameter of 20-40 microns. The patent vessels of the lung permit flow of the labelled particles to their respective capillary beds, where they temporarily lodge and provide an image of the perfused portions of the lung.

Ventilation Imaging

The ventilation portion of the study is based on the distribution throughout the pulmonary alveoli of an inhaled radioactive gas and its clearance during subsequent breathing of air, or the distribution throughout the pulmonary alveoli of an inhaled radioactive aerosol. Xe-133 is an inert gas, relatively insoluble, which distributes itself throughout the lungs in a uniform pattern in a patient with normal ventilation. 81 m Krypton is a generator-based, short-lived gas which is at present the best tracer for dynamic ventilation studies. Multiple projection imaging can be undertaken with it giving rapid images of high statistical quality.

Interpretation of the ventilation/perfusion (V/Q) study requires a chest radiograph obtained within a few hours of study. In the normal ventilation study, radioactive gases are uniformly distributed throughout both lungs on inspiration and at equilibrium and uniformly cleared from both lungs during the washout phase. Defects on the ventilation study indicate airway obstruction, which may be seen on any or all of the images. In obstructive airways lung disease, the 133 Xe fails to enter involved regions of the lung during the inspiratory phase, diffuses into those regions during equilibrium, and remains in those areas during the washout phase. Pulmonary emboli do not produce ventilation defects.

In the normal perfusion scan, radioactivity is uniform throughout both lung fields. Defects on the perfusion study may or may not match ventilation defects and chest radiography abnormalities. If the perfusion scan is entirely normal or if it shows small peripheral defects or only abnormalities that match ventilation defects, the patient probably (90-95%) does not have pulmonary emboli. If the perfusion scan shows defects that conform to anatomic lobes or segments of the lung, and if there are not matched by ventilation defects or chest radiograph abnormalities, the patient probably (80-90%) has pulmonary emboli. Between these interpretations is a range of instances. The clinical and laboratory information, in conjunction with a V/Q study providing an intermediate probability of a pulmonary embolus, may help one to decide.

Repeat perfusion scans can be helpful in verifying the impression of pulmonary emboli. Disappearance of the defects suggests pulmonary embolism. Significant resolution can occur in 48 to 72 hours and it is almost always apparent in 7 to 10 days.

Chronic Obstructive Airways Disease (COAD)

Emphysema is defined as parenchymal destruction distal to the terminal bronchiole with subsequent coalescence and over-distention of alveolar air spaces. Chronic bronchitis is associated with excessive tracheobronchial mucous production and recurrent cough. Both conditions may lead to a chronic obstruction of air flow. Ventilation/perfusion studies are probably more sensitive in detecting mild obstruction than standard pulmonary function tests. In the "washout" phase of the ventilation study, retention of xenon in the lungs beyond 3 minutes is abnormal and indicative of obstructive lung disease. In emphysema and chronic bronchitis, ventilation defects are often more marked than the corresponding perfusion abnormalities. Initially perfusion defects may be segmental in nature, but with progressive alveolar destruction and hyperinflation, a nonsegmental distribution is noted.

Lung Cancer

Bronchogenic carcinomas may cause perfusion defects on pulmonary scintigraphy due to compression of the adjacent pulmonary arteries. Corresponding ventilation abnormalities may be present if the tumour also compromises the bronchial tree. However, the degree of ventilatory impairment is usually less marked than the perfusion abnormality.

Cerebral Perfusion and Brain Scintigraphy

Pathophysiology

The exact mechanism by which the radionuclide localizes in areas of the brain that have undergone structural alterations is unknown. However, it is believed to be associated with the alteration in the blood-brain barrier at diseased sites, which allows the radionuclide to leave the blood and enter the region in relatively large amounts. In cerebral lesions, the primary factor responsible for disrupting the blood-brain barrier, thereby permitting radionuclide extravasation, is believed to be a structural alteration of the capillary endothelium.

The Normal Pattern of Brain Scintigraphy

The brain scan begins with an intravenous injection of ^{99m}Tc -glucoheptonate or ^{99m}Tc -DTPA (diethylenetriamine penta-acetic acid) and immediate collection of dynamic blood flow images at 1 second intervals from the time of appearance of activity in the carotid arteries through the cerebral venous phase.

The part of the study imaging cerebral blood flow usually yields one or two accurate arterial-phase images showing the carotid arteries, the circle of Willis, the anterior cerebral arteries, and the middle cerebral arteries. Uniform diffuse activity in the cerebral hemispheres indicates normal flow in the small vessels. The beginning of the venous phase is indicated by the appearance of the sagittal sinus. The static images obtained at a half to one hour show activity in the muscle of the face and neck, in the skull and scalp, and in the sagittal and transverse sinuses and the confluence of sinuses. The cerebral hemispheres in the static images show relative inactivity in the normal individual.

Cause of Abnormal Radionuclide Brain Studies

Neoplastic Disease

The overall sensitivity of radionuclide brain imaging in detecting brain tumours is approximately 70-85%. Tumours less than 1-2 cm in diameter are generally not detectable by this method.

Arteriovenous (AV) malformations, glioblastoma multiforme, meningiomas, and highly vascular metastatic brain tumours are often readily detected on dynamic and early static radionuclide images due to the increased vascularity associated with these lesions as well as alterations in the blood-brain barrier. In contrast, relatively avascular and slow-growing

tumours such as low-grade astrocytomas, pituitary adenomas, pinealomas, and medulloblastomas develop low-target/non-target count ratios and are not well identified.

Subdural Haematomas

These lesions may be characterized by an absence of peripheral activity on the flow study producing a flattened or even concave shape to the head on the involved side on the anterior or posterior view. On the static images, the same area shows increased activity. Increased peripheral activity on static images can also be seen in extradural haematoma, scalp oedema and haematoma.

Cerebrovascular Incident

Patients with this disorder often have a decreased flow pattern during the flow portion of the study and a wedge-shaped area of increased activity during the static portion of the study. A subarachnoid haemorrhage does not usually produce an abnormality on a brain scan unless the patient has a large aneurysm that would be visualized on the flow study or an infarct or intracerebral haematoma that might be seen on the static images.

Abscesses and Cysts

Patients with abscesses or cysts show an area of decreased activity on the flow study, but increased activity on the static images if a capsule has formed. Some cysts or abscesses have a clear central portion that has a "ring" or "doughnut" appearance.

Computerized Emission Tomography of the Brain

The arrival of single photon or positron emission tomographic images has added a new dimension to the instrumentation available for head scanning. These instruments allow for the recording of cross-sectional scans through a transaxial, coronal or a longitudinal plane.

New radiopharmaceuticals, such as N-isopropyl ¹²³I p-iodamphetamine, Tc-99m HM-PAO, Thallium 201 DDC offer a remarkable breakthrough in cerebral SPECT blood flow-scintigraphy. Nuclear medicine can now offer the clinician and surgeon a means of evaluating regional cerebral blood flow in a wide range of patients suffering cerebral disorders. Examples of disease conditions open to investigation include stroke, TIA, dementia, epilepsy, migraine, spasm following subarachnoid haemorrhage, trauma, evaluation of E-IC surgery, etc.

Cerebrospinal Fluid Scintigraphy - Cisternography

Upon injection into the subarachnoid space, usually via lumbar puncture, the radionuclide distributes itself in accordance with the basic flow pattern of the CSF. The tracer normally proceeds cephalad in the spinal subarachnoid space to reach the basal cistern within 2-4 hours. Flow continues upward around the cerebral convexities to reach the vertex within 24 hours.

Pathophysiology

Lesions which disturb the normal CSF circulation such as communicating hydrocephalus result in alteration in the flow pattern on radionuclide cisternography. However, conditions such as non-communicating hydrocephalus may be associated with a normal radionuclide flow pattern. Extravasation of CSF from the subarachnoid space indicates the presence of an abnormal fistulous tract and results in CSF rhinorrhea or otorrhea.

Renal Scintigraphy

Renal scintigraphy is performed to assess renal morphologic features and function, obstructive uropathy, and renovascular disease. Imaging is based on the concentration and excretion, by renal filtration and tubular mechanisms, of radiopharmaceutical agents that move through the renal cortex, collecting system, renal pelvis, ureters and bladder at convenient rates for imaging. Blood-flow images use agents that can be imaged during the first pass through the kidneys. Function and excretion images use agents that are rapidly concentrated and excreted. Obstruction is identified by the failure of radioactivity to pass from the superior to the inferior portions of the tract. Morphologic information is provided by agents that concentrate in the kidneys and remain long enough to allow background clearance for optimal imaging.

Dynamic Renal Imaging

After IV injection of Technetium-99m DTPA, this tracer is rapidly excreted by the kidneys. Due to the fact that there is little or no protein binding, tubular secretion or reabsorption, Tc-99m DTPA is excreted solely by glomerular filtration. DTPA is therefore an ideal agent for the evaluation of renal perfusion and glomerular filtration.

DTPA is also ideally suited for evaluation of the urinary drainage-collecting system - calyces, renal pelvis, ureters, and bladder. However, due to its minimal retention by the renal cortex, visualization for the cortex is less than optimal and it is not the best agent for evaluation of renal size or morphology.

Static Renal Imaging

Upon introduction to the blood stream, Tc-99m DMSA is predominantly bound in plasma proteins. As a result, there is essentially no significant glomerular filtration of DMSA. Marked uptake by the renal tubular cells of the proximal and distal tubules accounts for the finding that approximately 50% of the administered dose is localized in the renal cortex within 1 hour. The tracer is then retained by the kidneys for up to 24 hours. For this reason, DMSA is termed a renal cortical imaging agent.

Renogram

Iodine 131 and 123 Hippuran is an example of a renal function agent. Hippuran is rapidly cleared by the kidneys with a renal transit time of approximately 3-5 minutes. Hippuran has a dual excretory pathway with 20% excreted via glomerular filtration and 80% excreted via tubular secretion. This accounts for Hippuran's high first-pass extraction ratio of

90%. The symmetrical time activity curves generated by the passage of Hippuran through the individual kidneys reflect renal blood flow, function and urinary drainage.

Abnormal Renograms

Prerenal

- **Bilateral:** Poor cardiac output (failure) or dehydration may produce bilateral decreased renal plasma flow. Cortical transit is prolonged and excretion is reduced, due to the decreased rate of urinary flow.

- **Unilateral:** Unilateral renal-artery stenosis accounts for approximately 5% of cases of hypertension. Several renogram patterns may be observed depending on the degree of ischaemia.

Intrarenal

Essentially, there is a loss of glomeruli and nephrons resulting in a delayed time to peak and a prolonged excretory phase with resultant flattening of the renogram curve.

- **Tubular impairment:** In the early stages, tubular accumulation of the tracer is unaffected. In later stages, tubular uptake in addition to discharge is compromised. Thus renal cortical transit time and the secretory phase are prolonged and flattened. This flattened renogram pattern is characteristic of chronic parenchymal dysfunction regardless of aetiology.

- **Intrarenal obstruction:** Renal activity curves continue to rise for the entire length of the study as the tubules are unable to excrete the accumulated tracer due to obstruction. Renal images do not reveal urine within the pelvis as would be seen in cases of outflow tract obstruction. In addition, intrarenal obstruction is often bilateral in contrast to postrenal obstruction which is usually bilateral.

Postrenal

This category includes the obstructive uropathies in which the renal time-activity curves continue to rise for the entire study. Static images may reveal dilation of the collecting system proximal to the site of obstruction. Extrarenal causes of obstruction include ureteral stones, tumour and blood clot. In cases of chronic obstruction, the renal parenchyma may be irreversibly compromised, eventually resulting in parenchymal destruction and loss of the ability to accumulate hippuran.

Modified I-131-hippuran or, preferably Tc-99m DTPA renography may be employed to distinguish dilated nonobstructed systems (secondary to muscular atony, reflux, etc) from those with mechanical obstruction. If, at 15 minute post injection of either the tracer-marked pelvic activity persists, a diuretic such as furosemide is administered. Nonobstructed systems respond with a brisk diuresis and subsequent drop in activity. Mechanically obstructed systems show no response. This method of computer analysis of the outflow tract of the kidneys may be modified to detect the presence of uretero-vesical reflux. Images are obtained during and after voiding for this analysis. The reappearance or increase in activity in the

ureter or renal pelvis indicates the presence of reflux. This indirect method of assessing uretero-vesical reflux is somewhat less sensitive than direct radionuclide cystography, which entails catheterization of the bladder and subsequent instillation of the radionuclide. Residual-urine volume may also be calculated during this time by recording the activity, prevoiding and postvoiding, over the bladder.

Renal Perfusion Studies

The vasculature of the kidney can be studied by dynamic scintigraphy following rapid intravenous injection of a high-activity small-volume bolus of a short-lived renal-specific agent, such as Tc-99m DTPA.

Static Studies

Any of the agents mentioned previously may be used to obtain static renal images, although Tc-99m DMSA is the ideal renal-cortical imaging agent. Imaging with DMSA is performed at 2-4 hour intervals corresponding to the time when this agent achieves its peak renal accumulation.

Renal Imaging in Disease States

Neoplastic Disease

On static imaging, a neoplasm will appear as an area of focally decreased tracer accumulation. It is indistinguishable from defects produced by other focal lesions such as cysts, abscesses, infarcts, AV malformations, etc. When angioscintigraphy reveals increased perfusion of the lesion, it is most likely a vascular tumour (i.e. renal adenocarcinoma), although an AV malformation may present similar findings.

Inflammatory Disease

Pyelonephritis: In the acute stage, static images with any of the radionuclides may reveal enlarged kidneys which exhibit a generalized decrease in tracer activity. The chronic phase is characterized by the finding of a small scarred kidney with markedly decreased perfusion and minimal parenchymal function.

Abscess

Classically, abscesses present as focal areas of decreased tracer accumulation on static images and are avascular on perfusion studies.

Obstructive Uropathy

Initially, renal tubular function and blood flow are preserved. If, however, the obstruction is severe or prolonged, renal tubular function is impaired, resulting in a generalized decrease in parenchymal tracer uptake.

Vascular Disease

Renal artery stenosis, secondary to atherosclerotic changes or fibromuscular dysplasia, may be detected on the vascular flow studies. Captopril-induced unilateral changes in kidney function, as demonstrated non-invasively by radionuclide renography, can be used as a diagnostic method to detect renovascular hypertension caused by unilateral renal artery stenosis. In bilateral renal artery stenosis, the slopes of the ascending limbs for both kidneys will be reduced in comparison with that of the aorta.

Hypertensive Disease

Vascular flow studies reveal diminished renal blood flow while static images show decreased parenchymal activity reflecting impaired renal tubular function. These changes are usually bilateral.

Renal Vein Thrombosis

Classically, in renal vein thrombosis there is no renal blood flow and a lack of renal tracer accumulation on static studies.

Infarction

Commonly, embolic or atherosclerotic in nature, renal infarcts characteristically produce peripherally located focal areas of decreased tracer accumulation on static images.

Renal Insufficiency

The extent of renal functional impairment is reflected by the degree to which tracer accumulation in the renal cortex is diminished. Hippuran and DMSA are the best agents to assess renal morphology in instances of severe renal failure.

Renal Trauma

On static imaging, a contusion may cause a focal or generalized decrease in tracer accumulation with or without a corresponding perfusion defect on vascular studies. Laceration of the renal parenchyma may be visualized as a band of absent tracer activity on static images. In total avulsion of the vascular pedicle, scintiangiography reveals absent flow to the involved kidney and static images fail to visualize the kidney. Radionuclide angiography has been reported to have demonstrated posttraumatic AV fistulas and large pseudoaneurysms.

Congenital Anomalies

Static imaging may be helpful in detecting unilateral renal agenesis, hypoplasia, and supernumerary kidneys. The site of connection between horseshoe kidneys and their relative function can also be demonstrated on renal imaging. Bilaterally enlarged kidneys containing multiple defects are consistent with adult polycystic kidney disease. Characteristically, a multicystic kidney presents as a prominent area of decreased activity on perfusion and static radionuclide images.

Testicular Scintigraphy

Upon intravenous injection Tc-99m Pertechnetate becomes loosely bound to plasma proteins therefore reflecting regional tissue perfusion.

The testicular and deferential arteries provide the major vascular supply to the testes, epididymis and scrotum. Conditions associated with a relative hyperaemia such as inflammatory lesions (epididymitis and abscess) and certain vascular testicular tumours (seminoma) will demonstrate increased perfusion on scintiangiography and usually exhibit increased activity on the blood pool and static "tissue phase" images. Conditions that compromise the blood supply (such as torsion) cause decreased perfusion and diminished activity is noted on static images of the affected side. Relatively avascular lesions (such as cysts) are represented as areas of decreased activity on the static images.

Skeletal Scintigraphy

Approximately 60% of a radioactive phosphate-administered tracer is extracted by the osseous structures within 2-3 hours. The remainder is rapidly excreted in the urine. A small amount, 2-4%, localizes in the renal parenchyma.

Technetium-labelled phosphates are believed to undergo a process termed chemisorption in which the tracer is absorbed onto the surface of calcium hydroxyapatite crystals and then passes into the interior of the bone crystal. These radionuclides accumulate at metabolically active sites within the skeletal system. Deposition of the tracer occurs in areas of new bone formation of any etiology. Fully calcified mature bone takes up relatively little tracer. Skeletal lesions of any nature, however, can result in new bone formation and are therefore visualized as "hot spots" on bone scans. Bone scans are fairly nonspecific due to the fact that a large variety of conditions including infection, trauma, benign and malignant tumours, and metabolic disorders demonstrate increased radionuclide accumulation.

Bone Marrow Scintigraphy

Bone marrow scanning is used to determine the location and distribution of bone marrow and to detect bone marrow infarcts. It is based on the uptake of radiocolloid (Tc-99m Tin colloid) by reticuloendothelial cells in the bone marrow.

Bone marrow scans are usually done when radiation and chemotherapy have destroyed much bone marrow and when an assessment of the residual functioning bone marrow is needed before further therapy is undertaken.

Hepatic Scintigraphy

Colloidal (Tc-99m) particles are removed from the blood by cells of the reticuloendothelial system (RES) by phagocytosis. In a normal person, 85% of the RES cells are located in the liver, 10% in the spleen, and the remainder are distributed throughout the red bone marrow and lymph nodes. Cells of the RES are distributed homogeneously throughout the organs in which they are located. Maximum incorporation of radionuclide into RES cells occurs within 10-15 minutes.

In colloidal scintigraphy, an area of decreased hepatic activity may be caused by any condition which displaces, compromises the phagocytic ability, or reduces the vascular perfusion of the Kupffer cells. Conversely, areas of relatively increased activity may be secondary to increased regional perfusion, enhanced phagocytosis, or an increased concentration of Kupffer cells. Several possible mechanisms which may cause a reversal of the normal liver-spleen activity ratio with or without increased bone marrow uptake include: diffuse hepatic dysfunction, decreased hepatic perfusion and increased splenic or bone marrow perfusion.

Principal Causes of Focal Intrahepatic Defects

Neoplasm

- Primary
 - Hepatoma
 - Haemangioma
 - Hepatic adenoma and focal nodular hyperplasia
- Metastatic

Radiocolloid hepatic scintiangiography has a sensitivity of approximately 85% and a specificity of 75-80% in detecting metastatic disease. Metastatic disease may manifest itself as either single or multiple defects on static colloid studies. Carcinomas of the lung, breast, gastrointestinal tract and malignant melanomas represent the tumours which metastasize most frequently to the liver.

Infectious Disease

Focal infection: An abscess is noted as a focal defect on static radiocolloid imaging. On gallium imaging, the corresponding areas exhibit increased tracer accumulation throughout the lesion or localized at the lesion's rim.

A suspected subdiaphragmatic abscess on the right side may be evaluated with combined liver-lung scintigraphy, but gallium imaging should be used in cases of suspected left subdiaphragmatic abscesses due to the variable position of the spleen.

Benign Cysts

Whether single or multiple, as in polycystic disease, cysts present as focal defects on vascular and static tin colloid studies.

Trauma

Areas of hepatic laceration and haematoma formation are represented in the static and scintiangiographic colloid studies as regions of decreased tracer activity.

Major Cause of Diffuse Hepatic Disease

Cirrhosis

Initial changes involve fatty infiltration associated with hepatomegaly and mildly heterogeneous decreased tracer uptake. With progression of the disease, there is diffused inhomogeneous liver uptake, colloid redistribution with reversal of the normal liver spleen activity ratio and splenomegaly secondary to portal hypertension.

Hepatobiliary Scintigraphy

Metabolism and Distribution

Following intravenous injection, Tc-99m IDA (iminodiacetic acid) undergoes rapid clearance from the bloodstream. Most of the administered dose (85%) is extracted by the hepatocytes while the remainder is quickly excreted by the kidneys. IDA is handled by the hepatobiliary system in a manner similar to bilirubin. It undergoes quick polygonal cell uptake, conjugation, and excretion into the biliary ducts. In normal patients, the gallbladder, common bile duct, and duodenum are usually well visualized within 30-40 minutes. Sequential imaging thereby enables one to visualize the integrity of the system.

Pathophysiology

Diseases that affect hepatic perfusion, cause hepatocyte dysfunction or displacement, or cause cystic or common duct obstruction resulting in corresponding abnormalities in the scintigraphic images.

Biliary Scintigraphy in the Evaluation of Hepatobiliary Disease

Cholecystitis

Obstruction of the cystic duct is almost always present in acute cholecystitis, and this fact forms the basis for the scintigraphic diagnosis of this condition. In a patient with relatively normal hepatic function, failure to visualize the gallbladder despite imaging of the common bile duct and intestine, is abnormal and may be secondary to acute cholecystitis, chronic cholecystitis, or cystic duct obstruction without cholecystitis.

Cholestasis

While both functional and mechanical obstruction result in decreased hepatic uptake of Tc-99m IDA, hepatic accumulation at a given serum bilirubin level is more impaired by hepatocellular disease than by mechanical obstruction.

Hepatocellular Disease

This condition is characterized by decreased hepatic tracer accumulation, normal or delayed (within 24 hours) detection of tracer activity within the intestines, and lack of biliary tract dilation.

Extrahepatic Obstruction

Incomplete obstruction: Patients in the group classically reveal a dilated common duct and delayed (greater than 1 hour) appearance of tracer activity in the intestines. It is important to note that a patient with hepatocellular disease and a dilated common bile duct secondary to prior surgery may demonstrate a similar scintigraphic appearance.

Complete Obstruction

A lack of tracer activity in the gastrointestinal tract on delayed images up to 24 hours is considered diagnostic of complete extrahepatic obstruction. Rarely, very marked hepatocellular disease may produce similar findings.

Abnormalities on Hepatic Colloid Scintigraphy

Due to the fact that the Kupffer cells of the reticuloendothelial system are responsible for hepatic accumulation of Tc-99m tin colloid whereas uptake of Tc-99m IDA occurs via the hepatocytes, imaging of the liver with these two agents may yield different results. Hepatic abnormalities that present as focal areas of decreased activity on tin colloid scintigraphy but demonstrate normal or decreased tracer accumulation with Tc-99m IDA suggest several possibilities including hepatomas, hepatic adenomas, regenerative nodules in cirrhosis, intrahepatic gall bladder, or dilated intrahepatic bile ducts. In alcoholic liver cirrhosis the colloid scan shows diffuse decreased liver uptake with normal biliary function - although in the end stages of alcoholic liver cirrhosis both studies show markedly decreased uptake.

Splenic Scintigraphy

One of the major functions of the spleen is the sequestration and destruction of aged, abnormal, or damaged erythrocytes. Thermally denatured red cells are trapped by the spleen because they have lost the pliability necessary to traverse the mural fenestrations of the splenic sinusoids. Subsequent phagocytosis and destruction of the abnormal cells by the macrophages of the splenic reticuloendothelial system takes place.

Upon intravenous injection, thermally denatured radiolabelled erythrocytes are rapidly cleared from the blood stream and are homogeneously distributed throughout the spleen. Significant activity is present within the spleen 10-15 minutes following injection.

Whereas colloidal scintigraphy is based on the phagocytosis of particulate matter by cells of the RES, scintigraphy with denatured red cells is based on the unique ability of the spleen to sequester damaged erythrocytes. However, regardless of which agent is used for splenic scintigraphy, conditions associated with altered splenic perfusion, parenchymal dysfunction, or displacement will result in corresponding abnormalities on the scintigraphic image.

Abnormalities of Splenic Size, Position or Function

Splenomegaly

The upper limit of normal for splenic height and width in the posterior dimension is approximately 12 cm and 8.5 cm respectively. The major causes of splenomegaly are: neoplastic diseases, haematological disorders, infectious diseases, infiltrative diseases, collagen-vascular diseases, portal hypertension, trauma, etc.

Accessory Spleens

Found in approximately 10% of the population, accessory spleens are usually less than 1 cm in diameter and the majority are located in the splenic hilus or suspensory ligaments of the spleen. Accessory spleens represent normal splenic tissue capable of sequestering heat-denatured Tc-99m labelled red blood cells and phagocytizing colloidal radionuclides. However, they are frequently visualized on splenic scintigraphy in patients with a normal spleen due to their small size and hilar location.

Asplenia

Failure to visualize the spleen on splenic scintigraphy may be due to anatomic absence or nonfunction of the spleen.

Anatomic Absence

Congenital asplenia, also known as Ivemark's syndrome, is associated with absence of the spleen, midline position of the stomach and liver, pulmonary asymmetry, and cardiac anomalies. Splenectomy, of course, may also explain absence of the spleen.

Complete Nonfunction

Sickle cell anemia with repeated episodes of vascular thrombosis may eventually lead to total splenic infarction. Lymphoma has also been reported to cause complete nonfunction.

Diffuse and Focal Splenic Disease

Neoplastic Disease

Malignant: Lymphomas (Hodgkin's and non-Hodgkin's) and leukemic processes involving the spleen result in splenomegaly and cause focal or diffuse patchy areas of decreased tracer accumulation on static images.

Benign: Haemangiomas and hamartomas represent two fairly common benign tumours which present as focal areas of decreased tracer activity on static images, but show increased activity in the arterial or blood-pool phase of vascular studies.

Infectious Disease

Granulomas and abscesses present as avascular lesions on dynamic studies and are identified as focal areas of decreased tracer activity on static studies.

Vascular Disease (Infarction)

Arterial occlusion with resultant infarction of splenic tissue is most commonly secondary to arterial thrombosis as seen in sickle-cell disease or embolic phenomenon secondary to bacterial endocarditis, atrial mural thrombi, etc. Dynamic-flow studies classically reveal a peripherally located, wedge-shaped avascular zone which fails to accumulate radionuclide on static images.

Splenic Trauma

Usually secondary to blunt abdominal injury, splenic trauma may result in parenchymal contusion, subcapsular and intrasplenic haematoma formation, and splenic laceration or transection. Contusions and small haematomas secondary to minor trauma may be visualized as focal areas of minimally decreased activity on static images which resolve in 2-3 weeks. Classically, subcapsular haematomas present as a peripherally-located concave or wedge-shaped area of decreased activity in a patient with an enlarging spleen. Diminished or absent radionuclide accumulation in a linear or bandlike configuration is noted in cases of intrasplenic haematomas and splenic lacerations. The overall sensitivity and specificity of scintigraphy in detecting splenic trauma is approximately 90%.

The extremely uncommon situation in which splenic rupture is followed by the implantation of functional splenic tissue within the peritoneal cavity is called splenosis. These transplanted minispleens can be detected on splenic scintigraphy as areas of increased tracer activity distributed throughout the abdomen.

Thyroid Scintigraphy

Radiopharmaceutical Localization

Iodine-131

I-131 is the most widely used and the least expensive of the radiopharmaceuticals employed for thyroid imaging. The relatively long half-life of 8.05 days and the substantial beta emission makes I-131 an ideal agent for radioactive ablative therapy for the treatment of hyperthyroidism and thyroid carcinoma.

The greatest disadvantage of I-131 as an imaging agent is the high radiation dose due to the large amount of beta emission. This radiation adds no diagnostically useful information and may even cause some degradation of the final image. In addition, its 364 keV gamma emission is far above the optimal energy for the scintillation camera.

Iodine-123

Currently I-123 is not used because of its high cost, although its use may increase in the future as it is more readily available. The 159 keV energy of I-123 is ideal for detection by the scintillation camera and images of good quality can be produced because of the high target to non-target ratio.

Technetium-99m Pertechnetate

Tc-99m is a gamma emitter of 140 keV which is ideal for imaging with the scintillation camera. The high emission count rate improves image quality. Because Tc-99m is a pure gamma emitter, there is no beta radiation to the patient. The radiation hazard is further reduced by its short half-life of 6 hours. Therefore, Tc-99m is suitable for studies in children and young women. Delayed studies, however, are not feasible due to the short physical half-life.

Unlike iodine, technetium-pertechnetate is trapped by the thyroid but is not organified. Hence, discordant images may be seen when iodine and Tc-99m images are compared.

The normal thyroid exhibits a homogeneous distribution of radionuclide.

The radionuclide scan in diffuse toxic goitre reveals homogeneously increased activity of the entire gland. The gland is enlarged and has a lobular configuration.

In multinodular goitre the radionuclide scan reveals symmetric or asymmetric enlargement of a distorted thyroid gland. The margins of the gland are irregular and may be indistinct. There is a mottled heterogeneous radioisotope distribution, often with alternating areas of increased and decreased tracer uptake.

The possibility of substernal goitre must be considered in the evaluation of a mediastinal mass or a thoracic outlet syndrome. The diagnosis can be confirmed with radionuclide imaging, if the retrosternal goitre is functional thyroid tissue.

The presence of palpable nodules is the most common reason for obtaining a thyroid scan.

Thyroid nodules are classified by their functional status relative to the surrounding thyroid parenchyma. Hyperfunctioning or "hot" nodules demonstrate greater activity than the adjacent gland, whereas hypofunctioning or "cold" nodules demonstrate little or no activity.

Hyperfunctioning nodules or "hot" thyroid nodules with increased tracer activity, are usually benign. Benign adenomatous hyperplasia is the most common cause, accounting for approximately 90% of hyperfunctioning nodules. Nonpathologic anatomic variants, thyroiditis and hyperfunctioning normal tissue after surgery may produce a scan of similar appearance. Rarely, a malignant carcinoma may present as a hyperfunctioning nodule.

If only one lobe of the thyroid is seen on a scan, one must suspect the presence of a hyperfunctioning nodule with suppression of the contralateral side, prior surgical removal of a portion of the gland, or hemiagenesis (a rare occurrence).

The function of autonomous nodules is independent of TSH secretion. These nodules may produce high levels of thyroid hormone, which acts to suppress TSH production by the pituitary gland. The decreased level of circulating TSH in turn decreases function in the remaining normal thyroid tissue, thus accentuating the appearance of the nodule on the scan.

Hypofunctioning Nodule

Approximately 20% of hypofunctioning "cold" nodules are malignant, usually representing primary or metastatic carcinoma or lymphoma. Malignancy is more common in young patients and in those with a history of neck irradiation. Benign aetiology include cysts, adenomas, small areas of local thyroiditis, and early multinodular goitre.

Radionuclide scanning is often employed in evaluation of persistent hyperthyroidism or recurrence of a mass following thyroidectomy. Residual thyroid tissue or recurrent tumour may be demonstrated in this manner. In addition, metastatic foci of thyroid carcinoma elsewhere in the body may now become apparent although they were not appreciable prior to resection of the primary tumour. Metastatic foci may occasionally be demonstrated following the administration of TSH.

In Hashimoto's chronic autoimmune thyroiditis, the scan reveals an enlarged smooth contoured gland with heterogeneous radioisotope uptake. This heterogeneity, if extreme, may result in a pattern which may simulate one or more autonomous nodules and may pose some difficulty in the scan interpretation.

Radiation thyroiditis is a rare complication of I-131 therapy and may result in exacerbations of clinical hyperthyroidism and moderate cervical pain.

Radioactive Iodine Uptake

Iodide entering the circulation is removed from it by active transport into the thyroid cells and also by elimination from the body in the urine. If minimal or insufficient iodide enters the body over a long period, conservation is maximized and circulatory inorganic iodide is avidly taken by the thyroid. For this reason tests of thyroid function using radioactive iodine as a tracer must be interpreted in relation to local available dietary iodine.

The tracer radioiodide is usually given orally. The amount of radioactivity in the thyroid is measured at various times after the dose, the most useful single time being after twenty-four hours. The radioactivity measured at the selected time is related to the dose administered by appropriate calibration and recorded as a percentage of this.

In view of the influence of iodide repletion on uptake values a normal range must be quoted with caution, but a twenty-four-hour value in the range 20-30% of the administered dose would be normal in most populations. When this has been taken into account, a high uptake value is consistent with hyperthyroidism and a low value with hypothyroidism.

Gallium-67 Scintigraphy

Gallium-67 citrate has proven to be of the greatest clinical use in demonstrating the presence and extent of certain malignancies such as bronchogenic carcinoma, Hodgkin's disease and lymphoma. Active tuberculosis, sarcoidosis, abscess, pneumonia and pyelonephritis are among the inflammatory lesions that commonly result in a positive scan.

The clinical indications for Ga-67 are best understood when viewed from a metabolic perspective - since the specificity of Ga-67 for certain tumours appears to be largely a function of the metabolic activity of those neoplasms. An understanding of the activity of Ga-67 at the cellular level can help the surgeon to select those patients with tumours most likely to image successfully and to evaluate the clinical significance of positive and negative Ga-67 studies when they occur.

Shortly after intravenous administration, about one third of the Ga-67 is bound by plasma transferrin, haptoglobin and albumin. Renal clearance begins almost immediately with 12% of the administered dose excreted by that route during the first 24 hours. Twenty-six percent is excreted by the kidneys during the first week, while an additional 9% is excreted in the faeces. During the first 48-72 hour postinjection period, when scanning is normally performed, most of the Gallium-67 is concentrated in the liver, spleen and bones, and tumours or sepsis, if present.

The exact mechanism of Ga-67 concentration in tumours is still somewhat speculative. It may result from the localization in cytoplasmic lysosomes, lysosome-like organelles, or, perhaps, in the cell membrane.

Abnormal Ga-67 concentration is extensively documented in nonspecific inflammatory disease. Intracellular binding at such sites of inflammatory disease may be related to the activity of lysosome-rich macrophages and granulocytes.

Due to significant bowel excretion, serial scans with or without bowel cleansing are required to avoid false positive reporting in the abdomen. Normal salivary glands and breasts also concentrate this tracer.

Tumour Imaging

Identification of tumours has always been a cherished goal in radionuclide imaging. Various mechanisms have been explored, but none have had unqualified success. The most useful agent has been Ga-67. Almost any tumour may take up gallium, but the technique is limited by its variable sensitivity. The highest sensitivity has been in pulmonary carcinoma (80% to 95%) and in hepatoma (86 to 95%). Sensitivity in Hodgkin's disease is 87% overall, but it is only 50% for lesions inferior to the diaphragm.

Renal Gallium-67 Scintigraphy

Inflammatory disease of the kidneys results in uptake of Ga-67. Acute interstitial nephritis causes a diffuse, intense renal uptake of gallium that can be used to differentiate this condition from acute tubular necrosis. Ga-67 scanning may also be useful in the detection of

acute pyelonephritis; however, it is difficult to distinguish acute pyelonephritis from perinephric abscess.

Abscess Localization

⁶⁷ gallium-citrate scintigraphy is a useful scanning technique for this purpose. Whole body imaging will identify areas of pus collection (abscesses) which may remain undetected by any other means. When diagnosis of abdominal and pelvic abscess is sought, these areas are the most difficult to interpret.

Pulmonary Gallium-67 Scintigraphy

This study relies on Ga-67 uptake by areas of infection, inflammation, and neoplasm. Ga-67 scanning can distinguish active tuberculosis, with a 97% sensitivity rate, patients with inactive tuberculosis do not have a Ga-67 uptake. From 61 to 97% of patients with active sarcoidosis show Ga-67 uptake in pulmonary parenchyma or hilum, but many patients with inactive sarcoidosis also show Ga-67 accumulation; however, normal scan suggests the absence of disease. Many conditions cause diffuse pulmonary uptake of Ga-67 including pneumocystis carinii infection, bleomycin therapy, vascular talc granulomatosis in drug addicts, radiation therapy to the lungs, interstitial lung disease, and pneumoconiosis.

In children, Ga-67 citrate appears to be useful in differential diagnosis of acute osteomyelitis and cellulitis while in adults evaluating hip prosthesis infection and loosening is the main skeletal pathology benefiting from this technique.

Radionuclide Scintigraphy in Transplantation

Renal Transplantation

In the post-operative management of renal transplants there is a need for a method of diagnosing vascular insufficiency, acute tubular necrosis (ATN), rejection, and problems of the urinary outflow tract. All of these may occur separately or in combination, and all may be present as impairment of renal function with few specific features.

In the last few years, radionuclide scintigraphy has assumed an important role in evaluating these complications in renal transplantation. Following the proper bolus injection of a technetium-labelled radiopharmaceutical and computer processing of dynamic renal scintigraphy images, it is possible to show the difference between ATN and rejection by measuring patterns of blood flow. Generally, ATN is characterized by relatively normal blood flow whereas rejection is characterized by poor blood flow.

The most frequent complication, acute tubular necrosis (ATN), is secondary to ischaemia and is characterized by normal to high concentration of the radionuclide, but absence of any excretion. This pattern may be difficult to distinguish from obstruction in some cases, but ultrasound may assist in differentiating between these conditions. ATN usually manifests itself in the first several days after transplantation. In contrast to rejection, the abnormalities of ATN are transient and may show signs of resolution within several days.

In addition, perfusion is usually impaired to a lesser extent in ATN than it is in cases of rejection.

In hyperacute rejection perfusion and static studies demonstrate non-visualization of the kidneys and are identical to those obtained with thrombosis of the renal artery or vein.

Acute rejection of the transplant is usually characterized by poor blood flow to the transplant and poor radionuclide concentration and excretion. Consecutive studies may produce an identifiable pattern, as the abnormalities in rejection become progressively worse. As opposed to ATN, acute rejection classically occurs several days to weeks after transplantation and is associated with the development of fever and hypertension. The findings of an enlarged, tender kidney and decreased urinary sodium concentration are also noted. Oliguria is present in both entities, but is progressive in acute rejection. Scintigraphic differentiation of these two conditions may be accomplished with the use of Tc-99m fibrinogen, In-111 labelled platelets and Tc-99m sulphur colloid. These radionuclides demonstrate renal uptake in cases of rejection but not in ATN.

Renal artery or vein thrombosis is characterized by absent renal perfusion and total lack of tracer accumulation on the static images.

Obstructive uropathy may be secondary to blood clots within the collecting system or ureteral oedema, kinking, or ureteral compression due to lymphocele formation. Decreased vascular flow, diminished parenchymal accumulation of tracer, and radionuclide activity in a dilated collecting system are compatible with the diagnosis of obstruction.

When extravasation of urine from the collecting system occurs, it is usually within the first several weeks after transplantation and commonly involves the uretero-vesical anastomosis, the cystostomy site, or the mid-ureter. This extravasation may be noted by detecting urinary tracer activity outside the collecting system.

Cardiac Transplantation

First pass (FP) and multigated equilibrium blood pool ventriculography using the *in vivo* Tc-99m labelling of red blood cells (RBC) is used to measure left ventricular volumes (LVV) such as: stroke volume (SV), end-diastolic volume (EDV), end-systolic volume (ESV), and both global and regional ejection fraction (EF, REF). These studies have shown a very close correlation between the severity of the histological findings of rejection seen on endomyocardial biopsy and the measurement of LVV (SV, EV, ESV).

The diagnosis of acute rejection by radionuclide ventriculography has several advantages over the use of endomyocardial biopsy. The result is obtained within 30 minutes (compared with approximately 24 hours for the biopsy), it is without discomfort for the patient, can be repeated at frequent intervals, provides an absolute figure and objective indication of left ventricular function (compared with the subjective opinion of the histopathologist on a small and possibly non-representative piece of tissue).

The development of a premature and rapidly progressive form of coronary artery disease in the cardiac allograft has turned out to be an unanticipated sequelca of cardiac

transplantation. The disease leads to all the consequences of ordinary coronary artery disease, such as myocardial infarction, congestive heart failure, and sudden death, but is not associated with angina pectoris because of the lack of afferent reinnervation of the graft.

The greatest contribution of nuclear cardiology is in the discovery and vigilance in long-term follow-up of akinetic zones in the myocardial wall, which are not symptomatic and cannot be detected by other diagnostic means since it has been demonstrated that coronary arteriography shows no alterations while the postmortem examinations shows diffuse arteriosclerosis.

Miscellaneous Nuclear Medicine Procedures

Oesophageal Scintigraphy

The radionuclide oesophagogram (RNO) study monitors the transit of a radionuclide bolus, usually Tc-99m tin colloid diluted in water, immediately after a swallow until its arrival in the stomach.

Radionuclide oesophago-scintigraphy is a useful, safe, non-invasive and simple-to-perform functional test in the pretreatment and posttreatment management of oesophageal motility disorders like achalasia, diffuse oesophageal spasm, nutcracker oesophagus, oculo-pharyngeal muscular dystrophy, reflux oesophagitis, hiatal hernias, pharyngo-oesophageal diverticulum and malignant tumours of the oesophagus.

Gastroesophageal Reflux Study

The gastroesophageal reflux study is performed by oral administration of acidified orange juice containing 99m-Tc stannous colloid. As soon as the radioactive material has left the oesophagus, the patient is put into a supine position with a pressure cuff about the abdomen and the balloon centered over the epigastrium. Images of the stomach and lower oesophagus are obtained as pressure is applied in 20-mm Hg increments. If regurgitation into the oesophagus occurs before the 100-mm Hg mark has been reached, the study is positive and indicates gastroesophageal reflux. The technique is useful in the initial diagnosis of reflux oesophagitis, as well as in the quantitative evaluation of response to therapy.

Barrett's Oesophagus Study

In this anomaly, columnar epithelium replaces the stratified squamous epithelium which normally lines the lower oesophagus. The aetiology of this condition is uncertain. While it may be congenital in origin, many believe that it is often acquired due to its strong association with hiatal hernia and oesophageal reflux. If sufficient mucoid cells are present in the gastric columnar epithelium located in the lower to mid-oesophagus, this abnormality will be imaged on Tc-99m pertechnetate studies.

Meckel's Diverticulum (Ectopic Gastric Mucosa) Scintigraphy

Occurring in 1-3% of the population, Meckel's diverticulum is a blind pouch representing the remnant of the omphalomesenteric duct. Although commonly asymptomatic,

patients may present the signs of gastrointestinal bleeding (secondary to ulceration), acute diverticulitis, intestinal obstruction (secondary to intussusception), or chronic abdominal pain. The majority of patients are children less than 10 years old and there is a strong male predominance.

Tc-99m pertechnetate ion has been found to be accumulated and secreted by the mucoid cells of the gastric mucosa. These mucoid cells are responsible for producing a mucinous film which acts as an effective barrier by preventing the highly acidic gastric fluid from damaging the gastric mucosa. It is important to mention that a positive Meckel's study requires only the presence of parietal cells. Approximately 30% of Meckel's diverticula contain gastric mucosa and may therefore be visualized on pertechnetate studies. Cimetidine enhances the localization of gastric mucosa by preventing the secretion but not the uptake of pertechnetate by the gastric mucoid cells. Meckel's diverticulum is visualized as a small solitary focal area of increased activity commonly located in the right lower quadrant although it may be found almost anywhere in the abdomen. Characteristically, activity in the diverticulum appears at the same time as that in the stomach and the activity in both steadily increases during the course of the study.

Gastric Emptying Study

This test is performed by oral administration of either ¹¹¹In-DTPA in water, for measuring liquid gastric emptying, or ^{99m}Tc stannous colloid prepared in semisolid meal. Images are obtained at interval of 5 minutes, 15 minutes, 30 minutes and 90 minutes, and a computer is used to calculate the percentage of original activity left in the stomach. Normally, 50% of the liquid activity leaves the stomach in 30 minutes, and 50% of the solid activity leaves the stomach in 60 minutes. The test does not indicate the cause of the disorder but it is useful in confirming the diagnosis and in monitoring management.

Intestinal Bleeding Study

This examination is performed by intravenous injection of Tc-99m stannous colloid or TC-99m labelled red blood cells. Immediately after the injection, images are obtained every 1 to 2 minutes over the pelvis, for 10-20 minutes over the mid-abdomen. If no bleeding is seen, more superior images, including those of the lower liver and spleen, should be obtained, followed by left anterior oblique images. The study is continued for another 30 to 40 minutes, to allow bleeding hidden by the liver or spleen to move along the bowel into sight. If the patient moves his bowels during the study, the stool should also be imaged. Rectal or rectosigmoid junction bleeding may appear in the stools. If Tc-99m stannous colloid is used, one has only a short time during which to observe the bleeding because the colloid is cleared by the liver in a matter of minutes. If tagged red blood cells are used, one can image at various times up to 24 hours, but visualization of radioactivity in the intestines does not precisely indicate the point of origin.

Radionuclide Evaluation of the Portal Circulation

In order to study portal circulation a non-invasive method has been designed by administration of Thallium-201 per rectum.

When ^{201}Tl is delivered at the upper part of the rectum, it can be absorbed from the rectal lumen and the greater part of the radioactivity will proceed to the liver through the superior mesenteric vein, the inferior mesenteric vein and the portal vein in that order.

Normally, the liver can be visualized in less than five minutes after the administration of ^{201}Tl rectally whereas the other organs such as the heart, spleen and lungs are poorly visualized.

In patients with liver cirrhosis associated with portal-systemic shunt, and in many patients with hepatocellular damage, the liver is not so clearly visualized, whereas radioactivity in other organs, especially the heart, become evident.

Radionuclide Investigation of the Entero-Hepatic Circulation

(^{14}C) cholic acid, (^3H) cholic acid and their taurine conjugates have been used to study the intestinal absorption of bile salts under various pathological conditions. However, the use of ^{14}C and ^3H labelled bile acids presents certain disadvantages, not the least being the need to collect and process faeces.

SeHCAT (^{75}Se -23-selena-25-homotaurocholate) is the taurine conjugate of a synthetic trihydrocyl-bile acid, containing the gamma-ray emitting radionuclide ^{75}Se . Such a compound offers the possibility of a simple, novel and aesthetically acceptable method of investigating small-bowel disease, because it is absorbed exclusively and actively in the ileum, and has the physical and chemical properties not influenced by intraluminal factors.

Parathyroid Scintigraphy

Recently, a combined technique, utilizing technetium-thallium subtraction ($^{99\text{m}}\text{Tc}/^{201}\text{Tl}$) imaging for the localization of parathyroid adenoma in patients with primary hyperparathyroidism, has proved to be successful. This technique is based on the fact that the thyroid traps $^{99\text{m}}\text{Tc}$ and ^{201}Tl . In addition, it has been shown that parathyroid adenomas also take up ^{201}Tl . The accumulation of ^{201}Tl in a parathyroid adenomas is nonspecific and is most likely related to the cellularity or vascularity of the lesion. Thus, ^{201}Tl is administered to identify the thyroid and any parathyroid adenomas that may be present. Technetium-99m is administered to identify only the thyroid. The thyroid may then be removed out of the combined image by subtracting the $^{99\text{m}}\text{Tc}$ image from the ^{201}Tl image. Any remaining areas of ^{201}Tl concentration are probably markers for identification of parathyroid adenomas.

Adrenal Scintigraphy

The Adrenal Cortex

A number of radiolabelled cholesterol analogues are taken up by the adrenal gland during the biosynthesis of adrenal corticosteroids. Such modified cholesterol appears to be adequately utilized by the adrenal cortex in spite of the presence of the foreign atom in the molecule. Of the modified cholesterols, ^{131}I -19-iodocholesterol and ^{131}I -6-methylcholesterol

have proved most satisfactory. Another adrenal cortical radiopharmaceutical which has been clinically useful as an imaging agent is ^{75}Se -seleno-norcholesterol.

Adrenal scanning is valuable in differentiating tumour from bilateral hyperplasia in Cushing's syndrome, primary aldosteronism and adrenal androgen excess. It is also helpful in localizing medullary hyperplasia, and adrenal cortical remnants (after prior adrenalectomy) and in detecting unilateral hypofunction or disruption of the adrenal gland.

The Adrenal Medulla

^{131}I -MIBG (meta-iodo ^{131}I -benzylguanidine) is an exciting radiopharmaceutical with a high affinity for rare catecholamine-producing tumours, namely pheochromocytoma. The precise localization of these tumours can thus be achieved through scintigraphic images.

The molecular structure of MIBG has some similarities to the adrenergic hormone-neurotransmitter, noradrenaline. Noradrenaline is synthesized by normal adrenergic neurons and adrenal medullary cells, stored in adrenergic granules and secreted by exocytosis. Some of the secreted noradrenaline is taken up by the same adrenergic cells and stored again in granules. It is this uptake process that enables MIBG to enter into the pathways of noradrenaline. Although MIBG bears a guanidine side chain that resists metabolism, it still follows the pathways of noradrenaline into and out of adrenergic tissues.

After IV injection of radioiodine MIBG, normal whole body scintigraphic images show a faint tracer appearance in the salivary glands, spleen, liver, kidneys and bladder. Less frequently lung bases or colon can be visualized. This uptake is more prominent during the first 24 hours post injection, but diminishes progressively over the next 48 to 72 hours. At the same time, although only faintly, the normal adrenal medulla becomes evident as small, symmetrical focal areas of activity. Pheochromocytomas and other neural crest tumours and their metastases appear as dense focal areas of increased I-131 MIBG uptake.

As this radiopharmaceutical is concentrated in neurosecretory storage granules of chromaffin cells, it was to be expected that other tumours, which derive from the neural crest and are capable of production and storage of catecholamines, might also concentrate I-131 MIBG. Recent publications have described the uptake of this radiopharmaceutical by neuroblastoma, medullary thyroid carcinoma, paraganglioma and carcinoid.

Since the successful application of I-131 MIBG in the diagnosis of pheochromocytoma, it was recognized that this agent might deliver irradiation selectively to surgically unresectable tumours in a manner analogous to well-differentiated thyroid carcinoma treated with radioiodine.

Vascular Scintigraphy

Dynamic vascular radionuclide angioscintigraphy is done to evaluate vascular obstruction, aneurysms, and patency of vascular shunts and is based on dynamic flow of blood containing a radionuclide. Visualization of vascular flow depends on imaging of the bolus of radionuclide on its first pass through the vessels in question.

Vascular scans are performed by intravenous injection of Tc-99m pertechnetate or another Tc-99m radiopharmaceutical agent and by rapid sequential imaging over the area of interest. Computerized motion views are especially useful. For superior vena cava obstruction, simultaneous injections are usually given in both arms. The images are inspected for narrowing or complete obstruction of vessels. The images do not have the resolution of x-ray angiography, but the study is simple, non-invasive, and without associated morbidity.

Radionuclide Venography

The need for a simple, low-risk, easily interpretable test for lower extremity venous occlusive disease is evident. Of the currently available diagnostic tests, only contrast venography can be relied upon for accurate localization of proximal venous disease. However, contrast venography can lead to venous damage if contrast media is not adequately flushed out after the study. The risk of hypersensitivity reaction inherent in the intravenous injection of any contrast medium accompanies this procedure as well.

Radionuclide venography (RNV) fills the gap between the less specific noninvasive tests (radioiodinated fibrinogen uptake, Doppler ultrasound) and the more accurate but invasive technique of contrast venography.

Advantages of radionuclide venography are:

- It is technically simple and can be performed in conjunction with the perfusion lung scan.
- Simultaneous images of inferior vena cava, iliac veins, and femoral veins, as well as calf veins, can be obtained with a single injection.
- No significant complications from the procedure have been reported.
- It is suitable as a screening test for hospitalized patients or outpatients.
- The procedure takes less than 30 minutes and results are available immediately.

Radiopharmaceuticals that can be used for the diagnosis of thrombosis can be divided into four main groups:

- Radiotracers to study thrombogenesis.
- Radiotracers to detect clots already formed.
- Radiotracers with localization during thrombolysis.
- Radiotracers with no specific localization.

The radiopharmaceuticals of choice for RNV are Tc-99m-macroaggregate albumin and Tc-99m-human albumin microspheres.

Indications for the lower extremity venography are for:

- The detection of source and extent of venous thrombosis in patients with documented recurrent pulmonary emboli.
- The evaluation of leg veins in patients with signs and symptoms of venous thrombosis.
- A patient who is referred to the Nuclear Medicine Department for a perfusion lung scan and the patient has had a recent episode of pulmonary embolism or the patient belongs to the high-risk group for leg-vein thrombosis.
- A follow-up evaluation of efficacy of treatment in patients with extensive leg-vein thrombosis.
- An evaluation of previous surgical intervention, inferior vena cava umbrella or ligation.

Abnormalities in the radionuclide venography can be described as:

- An area of decreased or absent radioactivity flow corresponding to the region of thrombosis.
- Abnormal collateral flow.
- Stasis of radioactivity below the region of thrombosis.

Simplicity of the technique and reliability of 90% on average, make radionuclide venography with Tc-99m albumin particles the best routine procedure for detection of thromboembolic venous disease. Simultaneous visualization of the deep and superficial veins and imaging of the pelvic veins in lower extremity venography without additional injection are advantages of this technique. This is also the only procedure with which perfusion lung images can be obtained immediately after the venography without additional injection.

Lymphoscintigraphy

When colloidal particles are injected into intradermal or subcutaneous tissues, they traverse the lymphatic channels to the regional lymph nodes. Localization of particles in the lymph nodes depends on the integrity of the nodes and the patency of the lymphatic channels. Since direct intralymphatic injection is not required, the radiocolloid lymphoscintigram is applicable to many more anatomic sites than the contrast lymphogram.

Lymphoscintigraphic visualization provides:

- Evaluation of the status of nodes prior to arriving at a management decision.
- Accurate localization of nodes for optimum radiation therapy.
- Follow-up of patients in order to assess response to therapy or progression of disease.

The most frequently used tracer for lymphoscintigraphy today is Tc-99m antimony sulphide colloid (ASC), that has some characteristics which are superior to other technetium-labelled colloids. Imaging may start after the subcutaneous administration of 500 to 1000 microCi of Tc-99m ASC, with scans performed at zero hours for reference and at hourly intervals, depending on the nature of the investigation. Four hours after injection most of the lymphatics in the region are normally visualized.

Comment

Computerized Tomography

P Fourie

Computerized tomography (CT) was developed through the combined efforts of Alan Cormack (a graduate of the University of Cape Town), a research physicist at Harvard University, and subsequently at Tufts University, and Gordon Hounsfield, an electronic engineer working at the Central Research Laboratories of EMI in England. The first scanner was built by EMI and installed at the Atkinson Morley Hospital in London. Hounsfield and Cormack shared the Nobel Prize for Medicine and Physiology in 1979. Thereafter second, third and fourth generation scanners were developed. These advances led to shorter scanning times and better images. CT scanners are expensive and demand high maintenance costs and skilled technicians to maintain them.

Physical Principles

A well-collimated X-ray beam is mounted on a gantry which rotates through 180 degrees in early scanners, to 360 degrees in recent scanners, emitting successive X-rays which pass through the patient onto an array of detectors on the opposite side where the attenuated values of the X-rays are recorded. These values are then transmitted to a computer where they are stored.

The whole procedure is repeated at another angle and the data is again stored by the computer. This is repeated many times depending on the extent of the area which is being examined and on the number of such slices required.

The Fournier analysis is used to compute the acquired data into a mosaic of little squares called pixels, each with its own degree of density, which reconstruct a composite picture of a transverse section of the area examined. Each pixel represents the face value in density of a tiny block of tissue called a voxel. The number of pixels on a screen represent the matrix of that screen and is calculated as the square of the pixels in a line.

112 x 112 squared = matrix of 112 x 112

256 x 256 = matrix of 256 x 256

512 x 512 = matrix of 512 x 512

Each pixel has a density value expressed in Hounsfield units (HU). Thus, dense bone has a HU value of 1000 while water has a value of 0 and air as low as - 1000. The following table indicates some of the more commonly encountered HU measurements.

| | |
|--------------------------------|-----------------|
| Bone cortex | 250 to 1000 |
| spongy | 130 +/- 100 |
| Blood (clots) | 80 +/- 10 |
| Blood (venous) | 55 +/- 25 |
| Thyroid | 70 +/- 10 |
| Plasma | 30 +/- 5 |
| Exudate (more than 30 gm/L) | 18 +/- 2 |
| Transudate (less than 30 gm/L) | 18 +/- 2 |
| Ringer's | 12 +/- 2 |
| Water | 0 |
| Fat | - 10 to - 90 |
| Air | - 300 to - 1000 |

False Density Values

It must be borne in mind that density values are accurate only for structures that are larger than the actual tissue slice thickness. Structures that are thinner than the tissue slices cannot be measured accurately, if at all.

Hypervascular areas appear as hyperdense shadows on CT. Such lesions include:

- Neovascularization in neoplasms
- Inflammatory processes
- Vascular anomalies.

Hypovascular areas appear as hypodense shadows on CT - usually cysts, necrotic areas, haematomata and avascular tumours. The enhancement of surrounding tissues allows cysts to be better delineated.

The Density of Lesions

The density of lesions is graded into those that are hyperdense, isodense and hypodense. The density of organs or lesions can vary according to the pathological processes present. Examples are abundant but a few only will be mentioned.

Cysts

The percentage of protein in a cystic lesion will influence the density value of the cyst, for if the protein value is more than 30 gm/L, the density value will be 20-30 HU.

Blood

The intracorporeal protein value determines the density of the blood (viz 50 +/- 5 HU) in contrast to the haemoglobin which plays a minor role. Fresh blood clots (up to 7 days) will have higher density values. As the blood breaks down and the protein is absorbed the density values will fall substantially - even to levels of 0-5.

Abscesses

If liquefaction occurs densities may fall to +/- 30 HU or lower depending on the degrees of cystic density present.

Calcifications

These are readily demonstrated by CT, far more readily than with routine X-rays.

Artifacts

Unfortunately, these are a troublesome factor in some CT investigations. They are usually due to:

- The scanner itself.
- High-density objects in the field.
- Patient movement.

In this regard bowel movement can be reduced by the administration of glucagon or buscopan.

The gantry itself can also be tilted to 20 degrees on either side of the perpendicular in order to align the X-ray beam parallel to disc spaces or other structures which are not perpendicular to the horizontal line.

The high degree of resolution of the newer machines makes it possible to cut slices of 1 mm thickness, thus enabling imaging of even the inner ear.

Reconstruction

Reconstruction via the computer makes it possible to produce images in either coronal or sagittal sections of the area which has been scanned axially. In the case of the middle ear this is particularly useful. Three-dimensional reconstructions are time-consuming, but are of great help in planning reconstructive maxillo-facial surgery or surgery of facial trauma.

Dynamic Scanning

Six scans per minute can be performed during infusion of contrast enabling easier differentiation of tissues in the mediastinum particularly, as well as offering the opportunity to deduce physiological changes.

Contrast Media

There are a number of contrast media available ranging from air to relatively high-density iodine-containing preparations. Depending on the indications these can be given either by mouth, per rectum, intravenously, intrathecally or endobronchially.

When iodine-contrast materials are injected intravenously they disperse into the interstitial space causing a degree of whole body opacification. Thereafter they bind to proteins in the plasma and as such can be excreted via the liver to the bile and gastrointestinal tract. Finally they are excreted through the glomeruli into the urine. Passage through the blood-brain barrier causes enhancement of certain brain lesions which is then well-demonstrated on CT scans. The normal dose of iodine-containing contrast used is 40 g of iodine given over a 5 minute period followed by a further 2 g of iodine per minute.

The period of whole body opacification is important in evaluating the vascular anatomy of lesions as well as demonstrating hyperdense or hypodense areas in solid organs such as the pancreas, liver and kidneys. Furthermore bolus injections of contrast are useful in delineating large vessels in the mediastinum as well as in dynamic scanning of the abdomen. A portion of the contrast is filtered by the glomeruli through the tubules and later a smaller fraction appears in the urine. Vascular, tubular, pelvi-ureteric and finally bladder serial opacification therefore takes place. Bladder filling is particularly useful in delineating pelvic pathology.

For the investigation of the abdomen and the pelvis, outlining the bowel lumen is essential, and this is achieved by the use of water-soluble contrast media such as gastrograffin, usually given orally in a diluted form, but also given per rectum on occasion when the large bowel is to be delineated.

CT Myelography

Intrathecal injection of contrast followed by CT scanning is a useful investigation. Fractures of the base of the skull producing leakage of CSF is well shown when the contrast appears outside the normal thecal space. The presence of hydromyelia or syringomyelia can be demonstrated although this may require delayed scanning after 6 to 24 hours. The demonstration of pressure on the theca can also be well-demonstrated particularly in the lumbar region.

Air can also be used as a contrast material if injected intrathecally under sterile conditions.

Radiation Dose

The radiation dose received by the patient during CT scanning is usually less than that which occurs during comparable detailed procedures.

Preparation of the Patient

In general, it is preferable that the patient be kept fully informed of the nature of the examination, as his/her co-operation is essential during the procedure. This involves the intermittent cessation of respiration, absence of movement of the portion being examined and the notification by the patient of any undue discomfort that may be encountered, particularly after contrast administration.

Interventional Radiology

Computerized tomography (CT) can be utilized in the percutaneous drainage of abscesses and other interventional procedures. This may be required when accurate visualization of the abscess or cyst is impeded by air or gas during ultrasound investigation. Particularly in the lung where needle biopsy through surrounding air makes ultrasound investigation impossible. Some retroperitoneal lesions can also be detected by CT and biopsied. Similarly intramediastinal and pelvic masses near bone are better delineated and localized under CT imaging. Furthermore liver lesions near the diaphragm are often better visualized by CT and biopsies taken without fear of causing a pneumothorax.

The drainage of abscesses with assistance of CT imaging is well described.

Radiotherapy

CT is extensively utilized in the staging and planning of therapeutic procedures, and follow-up after surgery, radiotherapy or chemotherapy for malignant disease.

Problem Areas

Patient co-operation is important to produce good CT images and in this regard children and restless patients are a problem. Adequate sedation is essential. Furthermore where patients are short of breath, it may be impossible for them to hold their breath for the required 5 seconds during the exposure. Where general anaesthesia has to be resorted to, it becomes impossible to feed the patient oral contrast material, thereby limiting the scope of the CT examination. In the case of children shorter scanning times are possible, thus allowing adequate scans to be performed under limited sedation. This is particularly the case where tumours of the new-born are concerned. The normal ratio of 2-3 mL of copntrast per kilogram of mass is applied using 60% iodine contrast medium given either as a bolus or an infusion over 20 minutes.

Occasionally the size of the patient does not allow his bult to fit into the gantry thereby making examination impossible.

Summary

Computerized tomography can be used in the examination of practicallyt every organ or tissue of the body. CT is one of the modalities which has produced the greatest advance in diagnostic radiology since the original discovery of X-rays in 1885. However, since CT scanning has become so readily available there is a danger that the modality may be utilized in cases where an alternative and cheaper method of diagnosis is available. Therefore the clinician should be aware that the examination is expensive and that potentially harmful radiation is utilized.

CT is an excellent tool to demonstrate brain lesions while in other organs it can be of great benefit. The disadvantage of CT is that it cannot always distinguish between benign and malignant lesions. Furthermore, depending on the size of the slices used during the examination, it is possible to miss lesions of up to 2 mm in size in the abdomen and pelvis

nad occasionally in the lungs. Minimal enlargement of lymph nodes will also not be detected. In the gastrointestinal canal the thickness of the bowel wall can be shown but mucosal lesions are beyond the scope of the modality.

Time alone will show what the role of CT scanning is compared to magnetic resonance.

Ultrasound

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Introduction

Any soft tissue can be examined with ultrasound provided bone, air or gas is not present on the path of the transmitted soundwave.

Some of these obstructions can be overcome:

- By starving the patient overnight
- By using a sector transducer to examine the heart through the intercostal spaces
- By filling the bladder to examine the pelvis.

Gastro-intestinal examinations remain unreliable.

Soft tissue masses are localized first, in relation to *body surface*, which is ideal for aspirations or biopsies and, second, in relation to *surrounding anatomy*.

One of the most valuable uses of ultrasound is to distinguish between solid and cystic masses. Because ultrasound is harmless, and comfortable for the patient examinations can be repeated often to monitor the size of masses or cystic areas of patients on treatment.

To arrive at a diagnosis the ultrasonography examines many two-dimensional "slices", in several different planes, tilts and sensitivities knowing the anatomical location of each scan. Much of this information is stored in the ultrasonographers mind as a three-dimensional image. In short, a complete diagnostic process has taken place of which little can be gleaned from a few illustrative cuts. Small wonder that those not attending the investigation experience difficulty in making a diagnosis from a few selected photographs.

Physics of Diagnostic Ultrasound

In medical diagnostic ultrasound the puls-echo technique is used. Information is reflected back toward the source that generated the energy. The reflection technique consists of pulsing a crystal (commonly lead zirconate titanate) and sending energy into the patient. These pulses of energy are reflected at different interfaces inside the patient. Most of the

energy passes through the various interfaces to penetrate deeper into the patient, but at each interface a small percentage of energy is reflected back toward the transducer.

On reaching the transducer the reflected wave is translated by the transducer into a very small voltage. Therefore, the ultrasound transducer acts as both a transmitter and a receiver of sound. This is made possible by the piezoelectric properties of the transducer, which take effect when a pressure wave compresses the surface of the crystal in the transducer and causes it to give off a voltage on its surface. The piezoelectric effect occurs when the transducer is acting in the receiving mode and the reverse piezoelectric effect occurs a voltage is applied to the surface of the crystal causing the crystal to expand and give off a pressure wave that passes into the patient if the crystal is in contact with the person.

Energy is pulsed into the patient for only 5-6 microseconds and is dampened quickly. This is less than 0.6% of the time. The transducer receives reflected echoes from within the body for approximately 0.26 milliseconds or 26% of the time. The receiving time is followed by a quiet time in which there will be hardly any echoes returning to the transducer until the next pulse. This is approximately 0.74 milliseconds or 74% of the time.

The listening period is long enough for all the echoes within the body to have adequate time to reach the transducer without interference from reflected echoes from the next pulse. Because of the short pulsing time (0.6%) very little energy is sent into the patient during the time the transducer is on the patient's skin. The long listening period (99.4%) makes real-time scanning, which is used nowadays possible.

High-frequency ultrasound cannot penetrate as deeply as a lower frequency. Therefore, low-frequency transducers (i.e. 2.25 MHz and 3 MHz) are used for deep organs and the high-frequency transducers (i.e. 5 MHz to 10 MHz) for superficial structures and small parts including the thyroid, parathyroids, testicles and penis.

There are two methods of generating the real-time image. The transducer is mechanically oscillated or, as with the phased-array transducer, many small transducers arranged in an array are electronically steered and focused.

Ultrasonography of the Abdominal Cavity

In the evaluation of abdominal masses and fluid collections, sonography retains an important place. An accurate differential diagnosis is possible with ultrasound but a final diagnosis usually requires biopsy, aspiration or other confirmatory studies. The intelligently aggressive use of ultrasound can often limit morbidity and the cost of diagnosis. However, one must remember that other studies such as computed tomography (CT) or magnetic resonance imaging (MRI) may provide a more accurate or complete understanding of the problem under certain circumstances even if it is more expensive.

General indications for sonographic study of the abdominal wall and cavity include:

- Definition of the origin, extent and character of a palpable mass lesion
- Detection and characterization of intraperitoneal fluid collections
- Guided aspiration, biopsy, and drainage procedure.

Pathological Conditions in the Abdomen

Masses and fluid collections may arise in or involve the subcutaneous plane, musculofascial plane, peritoneal surface or intra-abdominal compartment. After localization the internal consistency of the abdominal mass is considered, which assists in the differential diagnosis.

Abdominal Wall

Cystic areas limited to the abdominal wall usually include seromas, abscesses and haematomas. Rarely, a cystic or necrotic tumour may be present. Solid areas include tumour, clotted blood, indurations, desmoid tumour and malignant fibrous histiocytoma. Aspiration can confirm the diagnosis.

Fluid Collections in the Peritoneal Cavity

The significance of a fluid collection is usually determined by the clinical setting and aspiration.

Fluid accumulations in the peritoneal cavity as seen on sonography may be free, loculated or contained in the bowel.

Free fluid may be either simple or complex. Complex fluid collections have some sort of internal echo pattern such as septae or floating debris.

Localized Peritoneal Abnormalities

After the origin and extent of a peritoneal abnormality have been studied and it has been determined that the abnormality is most likely a localized disease, the sonographic features of the localized mass or fluid collection can be scrutinized.

Ultrasound is best suited to the detection of fluid collections in the subphrenic spaces, subhepatic space, paracolic gutters and true pelvis. Abdominal wall, liver and splenic abscesses are also detected with 90-95% accuracy on ultrasound. The middle and lower abdomen and other areas are best studied with CT. However, while detection rates are high ultrasound often may not provide all the information necessary for management. If high quality ultrasound is not available, use CT as the screening examination.

Bowel

In diseases of the stomach and of the small or large intestine the diagnostic value of conventional abdominal sonography is limited. This is due to the presence of gas within the bowel that limits full sonographic evaluation of the bowel wall which makes the interpretation of diseases of the bowel wall both difficult and inexact.

For evaluation of gastrointestinal tract, confirmation of abnormal bowel patterns is absolutely necessary. At times suggestions of abnormalities are only seen fleetingly. However

if the pseudokidney sign or sonolucent mass is of real significance it will be persistent during the course of the examination.

The pseudokidney sign is a term developed to indicate a definite and persistent mass consisting of a strong echogenic centre (presenting the mucosa) surrounded by a sonolucent rim (presenting the muscle wall). Other terms are halo, target, cascade, doughnut or ring. This is seen in conditions such as:

- Regional enteritis
- Intussusception
- Lymphoma
- Carcinoma
- Metastatic disease
- Appendiceal abscess
- Ischaemia
- Intramural haematoma

The common link of all these abnormalities is bowel-wall thickening. The normal sonolucent rim should be less than 5-7 mm. A sonolucent rim more than 8 mm should raise suspicion of pathology.

The second pattern of bowel abnormalities found is a tubular sonolucent mass. These masses most frequently correspond to dilated fluid-filled loops of the bowel and occur in conditions such as ileus, bowel obstruction secondary to adhesions, carcinoma and other obstructive masses. Peristaltic movements should be monitored.

The persistence of these masses on real-time should alert the examiner to potential pathology.

Acute Appendicitis

The examination is performed using a 5 mHz linear transducer and compression is applied over the appendix area in order to remove overlying intraluminal gas. The appendix area is then reduced to a small space between the anterior abdominal wall and the psoas muscle and is antero-lateral to the iliac vessels.

The acute appendix can be demonstrated as a tubular structure (3-10 mm long) with one blind end - or as a round (doughnut sign) structure - consisting of an outer translucent layer (muscle) and inner echogenic layer (mucosa) with or without central fluid or solid material (fecolith). No peristalsis can be demonstrated in this tubular structure and the

abnormal rigid appendix cannot easily be compressed. Complications of acute appendicitis can be demonstrated by the following findings:

- Marked dilation of the lumen caused by pus under pressure
- Periappendicitis seen as an echopoor area around the appendix
- Local pus pockets around the perforated appendix
- Enlarged mesenteric lymphnodes
- Free fluid in the peritoneal cavity including the subhepatic space or in the pouch of Douglas or more localized intraperitoneal fluid collections representing abscesses.

Abdominal Ultrasound

Real time imaging is currently the principal mode in abdominal sonography.

Liver

Because few hepatic lesions have specific sonographic features, knowledge of the patient's clinical history as well as the usual sonographic patterns of various lesions are important.

Indications for Liver Sonography

- Assessing the liver size
- Evaluating anomalies and form variations
- Detecting and evaluating diffuse hepatic pathology
- Locating primary tumours and metastases and monitoring the course of therapy
- Ultrasound-guided needle biopsy or fine needle aspirations

Limitations

- Subdiaphragmatic portions can only be visualized by longitudinal intercostal or oblique subcostal scanning - for this reason a sector real time transducer is preferred.
- Visualization may be difficult when an elevated diaphragm or right-sided phrenic nerve paresis is present.
- Even large tumours may be missed if the echo pattern and density is the same as that of the surrounding liver tissue.

Normal Dimensions

Measurements taken along the central surface in the mid-clavicular line $11 \text{ cm} \pm 1 \text{ cm}$ and with sector scanning up to 13 cm. Maximum thickness of the left hepatic lobe is 5 cm.

Preparation

Fasting is required to try and control excessive intestinal gas.

Hepatic Pathology

In the following paragraphs, sonographic patterns of disease are reviewed as an aid to limiting the differential diagnosis in patients with hepatic abnormalities.

Benign Localized Lesions

Hepatic cystic lesions: Sonographically, cysts have thin, well-defined walls, are echo free, and show distal sonic enhancement. Complications such as haemorrhage may occur, causing some changes in the sonographic pattern, and calcification may occur in cyst walls.

Inflammatory Lesions

Pyogenic abscess: Sonographically, most pyogenic abscesses are round or oval with poorly defined walls. They tend to be centrally located. Internal echogenicity is usually less than that of the surrounding parenchyma. Gas-containing abscesses may be diffusely hyperechoic.

Amoebic abscess: Sonographically, most amoebic abscesses are peripheral, touching the liver capsule. They have well-defined margins but without prominent wall echoes. Almost all amoebic abscesses show some distal sonic enhancement.

Hydatid cyst: Lesions may be purely cystic, mixed, or solid. Calcifications are frequently present. Diagnosis depends on appreciation of the sonographic findings and correlation with clinical findings.

Traumatic Lesions

Hepatic haematomas: The sonographic appearance of blood varies with time. Acute hepatic haemorrhage is generally echogenic and this will persist for one to several days. Over a period of weeks, clots may either disappear or lyse completely, leading to an almost totally echo-free collection. Some dependent sludge-like material is frequently seen.

Seromas and post-traumatic bilomas: Bilomas develop over a period of several weeks due to gradual bile leakage from small duct injuries. They are generally total echo free and exhibit striking distal sonic enhancement.

Benign Tumours of the Liver

Cavernous haemangiomas are the most common benign neoplasm of the liver. They tend to be well-defined, highly echogenic lesions. Unfortunately, a spectrum of sonographic findings may be present.

Liver cell adenomas are usually well-defined lesions that exhibit slightly increased echogenicity compared to surrounding hepatic parenchyma but other sonographic patterns are also common. Focal nodular hyperplasia has a variable ultrasound appearance.

Small echogenic foci: Intrahepatic stones, intrabiliary and intravascular gas, and dystrophic calcifications may all cause shadowing echogenic foci within the liver. The differential diagnosis can usually be made by correlating the clinical diagnosis with the sonographic findings.

Focal Malignant Disease

Sonographically, hepatocellular carcinoma has no specific appearance. It is difficult to differentiate from metastatic disease, as both are frequently multifocal, occurring in all lobes of the liver. When small (< 3 cm), hepatocellular carcinoma are usually well-defined, hypoechoic, relatively homogeneous masses. Hepatic metastases cover the sonographic spectrum from purely cystic to diffusely hyperechoic. A diffuse parenchymal pattern may also occur with metastatic disease.

Other Malignant Tumours

Cholangiocarcinoma: Being infiltrative tumours they are usually not imaged, but proximal intrahepatic biliary dilatation is noted. Increased peribiliary echogenicity or, rarely, a peribiliary mass may be demonstrated. Hepatic involvement by lymphoma is common in late stages, but detection remains difficult because of diffuse infiltration. When focal lesions occur, they tend to be hypoechoic or even anechoic, but other patterns are also seen. Calcification in hepatic metastases is commonest in mucinous adenocarcinomas, most often arising from the colon.

Diffuse Hepatic Disease

The sonographic findings in diffuse hepatic diseases are not specific. Diagnosis is difficult in all forms of hepatitis. Cirrhosis usually causes diffuse increased echogenicity as well as alterations in shape due to atrophy and hypertrophy and it may be difficult in some cases to differentiate between metastases and cirrhosis. Fatty infiltration may cause increased echogenicity indistinguishable from cirrhosis. Diffuse tuberculosis may cause a "bright liver". Once again, correlation with clinical findings is important in establishing the diagnosis.

The Gallbladder and Biliary Tract

Because of its high sensitivity and accuracy in detecting gallstones and for determining biliary dilatation, ultrasound is likely to remain the examination of choice for evaluating both jaundiced patients and those suspected of having cholelithiasis.

Diagnostic Value

A normal gallbladder should be visible in virtually all patients especially if it is physiologically distended after an 8 to 12 hour fast. The shape of a typical gallbladder is oval or gourd-like, but frequently it varies from this configuration and contains apparent folds or kinks. Any fold in the gallbladder can produce high-amplitude echoes that may be associated with posterior acoustic shadowing (due to refractive effects).

Normal Dimensions

Gallbladder: 6-7 cm x 3 cm x 2 cm. Maximum 10 cm in length, 4 cm wide and volume not exceeding 200 mL.

Maximum wall thickness: 3 mm (including when contracted).

Intrahepatic biliary tracts: Usually thin, filiform, elongated.

Extrahepatic biliary tracts: Up to 5-6 mm or less (max 7 mm).

Postcholecystectomy: Up to maximum of 10 mm.

Gallbladder Pathology

Cholelithiasis

Ultrasound is the method of choice in the diagnosis of cholelithiasis. Because gallstones both absorb and reflect the ultrasound beam, the sonographic effect is a highly reflective echo originating from the anterior surface of the calculus with a prominent posterior acoustic shadow. The demonstration of a posterior acoustic shadow is important. Stones as small as 3 mm are detectable.

Wall Changes

The most frequent gallbladder wall abnormality detected is diffuse thickening, which is diagnosed when the wall is more than 3 mm thick. Diffuse wall thickening is now recognized as neither sensitive nor specific for an inflammatory process. Focal gallbladder wall thickening however suggests primary gallbladder pathology.

Sludge

Echogenic bile or "sludge" is particulate material (specifically calcium bilirubinate and/or cholesterol crystals) within bile. Sludge characteristically displays low to mild-level echoes and it is not accompanied by posterior acoustic shadowing.

Acute and Chronic Cholecystitis

The most sensitive sonographic criteria for diagnosing acute cholecystitis are the presence of gallstones and focal gallbladder tenderness. Other findings that corroborate the

diagnosis include gallbladder dilatations, sludge and wall thickening. Chronic cholecystitis is diagnosed if the gallbladder contains stones but the secondary criteria are missing.

Pericholecystic Fluid

Is most often due to acute cholecystitis, complicated by gallbladder perforation and abscess formation and is sonographically demonstrated as an anechoic or complex fluid collection adjacent to or surrounding the gallbladder.

Intrahepatic Bile Ducts

Under normal circumstances, only portal veins are visible within the portal triads. When intrahepatic bile ducts dilate, they cross the threshold of visibility and the most important sonographic feature is irregularity of the walls of the dilated bile ducts.

Extrahepatic Bile Ducts

The primary function of ultrasound is to determine whether or not biliary obstruction is present. A secondary function is to determine the level and cause of obstruction, if possible. Extrahepatic dilatation occurs before intrahepatic dilatation. Levels of obstruction are intrapancreatic obstruction, suprapancreatic obstruction and porta hepatis obstruction.

Choledocholithiasis

Often detectable only by dilatation of the biliary tract. The occluding stone is usually in a prepapillary location, obscured by air in the duodenum. Diagnosing stones in the proximal common bile duct is \pm 90% sensitive.

Pancreas

Diagnostic ultrasound enables direct visualization of the pancreas. Tissue echogenicity is an important aid in differentiating various masses. Adequate visualization is often obscured by ribs, stomach gas or colon gas.

Technique for Pancreatic Ultrasound Examination

The left lobe of the liver is used as an ultrasonic window for visualization of the pancreas. Since air within the stomach or bowel may obscure sonographic viewing of the pancreas the patient is preferably examined early in the morning and kept without oral intake overnight. The pancreas is usually as or slightly more echogenic than the liver. Fatty deposition within the pancreas and the patient's age are major factors contributing to increased echogenicity of the pancreas. In the pancreatic parenchyma the pancreatic duct may be visualized as a single linear echo or a small tubular structure (size 2-3 mm). Because of air in the left upper quadrant, the pancreas tail is difficult to visualize. A fluid-filled stomach may act as an ultrasonic window. The head and body of the pancreas is seen in approximately 70-80% of cases, while the tail is seen in approximately 30-40% of cases.

Ultrasound and CT Evaluation of the Pancreas

Recent studies have shown that CT has a higher sensitivity and diagnostic accuracy than ultrasound in detecting pancreatic pathology. The obvious advantage CT has over ultrasound is in the region of air and bone.

Pancreatic Pathology

Pancreatitis

Acute pancreatitis may be diffuse or localized. The ultrasound changes in pancreatitis involve increased size and decreased echogenicity, due to oedema.

Chronic pancreatitis can be diffuse or localized. The pancreas will have an irregular echogenic appearance due to fibrosis and early calcifications. The borders are often irregular and distinction from neoplasm is extremely difficult.

Pancreatic Pseudocysts

Pseudocysts occur in approximately 12-20% of patients with acute pancreatitis. Pancreatic pseudocysts are mainly sonolucent masses. Their borders are highly echogenic and somewhat thicker and more irregular than simple cysts of kidney or ovary. They may be unilocular or multilocular. With ultrasound we can serially follow the development and evolution of pancreatic pseudocysts.

Pancreatic Abscess

The sonographic appearance depends on the amount of suppurative material and debris present. The walls of an abscess are usually thick, irregular and highly echogenic.

Pancreatic Neoplasms

The normal cobblestone appearance of the pancreas is lost and replaced by a less echogenic, coarser mass. There is enlargement of the pancreas and often an irregular, nodular border. Ultrasonographic detection of a neoplasm is easiest in the pancreatic head, where displacement of numerous surrounding vessels is often noted. Tumours of the tail are more difficult to detect because of air in the stomach and colon. They are often best seen through the left kidney or the spleen. Peripancreatic adenopathy can often be confused with pancreatic masses. Lymphadenopathy usually presents as a relatively lucent mass on ultrasound, similar in appearance to pancreatic carcinoma.

Percutaneous aspiration under ultrasonographic guidance has been found to be useful in the diagnosis. Ultrasound may also be of assistance in planning radiation therapy and in following up tumour response.

Ultrasonography of the Spleen

It is included in all routine abdominal sonograms. A 3.5-5 MHz high-quality real-time sector scan is used

The Normal Spleen

Normal size is 11 x 7 x 4 cm. A left lobe of the liver insinuated between the spleen and left hemidiaphragm should be distinguished from a subscapular haematoma or subphrenic abscess. The stomach containing air or fluid can be shown within the centre of the spleen and must not be misdiagnosed as a splenic abscess or haematoma. With a mass in the left upper quadrant it helps if the spleen is demonstrated separately.

Pathology of the Spleen

Splenomegaly

Ultrasound is the method of choice to determine spleen size, and is used to monitor spleen size in the course of systemic or infectious disease. Generally the aetiology of splenomegaly cannot be established. Other findings to establish portal hypertension as the cause are recanalization of the umbilical vein, other portosystemic collaterals and ascites. It helps to identify other evidence of lymphoma such as lymph-node enlargement or liver involvement.

Focal Abnormalities

Ultrasound can diagnose lymphomatous involvement, metastases, cysts, haematomas and primary haemangiomas. Focal solid lesions suggest primary involvement with lymphomas, or metastasis, most commonly secondary to malignant melanoma. No type of primary is associated with a specific appearance of focal lesions, and the characteristics of a lesion can change after chemotherapy or radiation therapy. An abscess and simple cyst can be differentiated. A cyst with a calcified rim suggests the possibility of an echinococcal cyst. Focal calcifications because of old granulomatous disease, most commonly tuberculosis and histoplasmosis, may be similar in appearance as gas in an abscess. A plain film or CT scan can then easily differentiate between them. Suspected splenic infarcts should be followed up to show a decrease in size of the lesions to confirm that they are benign and probably infarcts.

Splenic Trauma

Ultrasound is highly accurate in diagnosing splenic trauma. One can distinguish between an intact capsule with intraparenchymal or subcapsular haematoma, and a ruptured capsule with a fluid space separate from the spleen. Immediately after trauma it is easy to identify a haematoma, but very soon and for the next 24-48 hours, the blood clots and the echogenicity is either the same or denser than the surrounding normal splenic parenchyma. A sonogram after 2-3 days will demonstrate liquefaction of haematomas. If, with the help of the clinical situation, one cannot distinguish between perisplenic haematoma and abscess, fine needle aspiration can be performed.

Congenital Abnormalities

Isotope studies are better to confirm the absence or presence of splenic tissue.

Renal Ultrasound

Renal Pathology

Normal kidneys are visualized in nearly 100% of cases. The normal length is 10-12 cm. The kidney can be evaluated for anatomic abnormalities, pseudotumours and pelvic lipomatosis. With Doppler Ultrasound and dynamic scanning, renal blood-flow alterations can be studied. Possible causes of haematuria can be elucidated. Renal and juxtarenal tissue can be imaged.

Congenital Anomalies

Sonography can detect malformed, anomalous and ectopic pelvic or thoracic kidneys. It can distinguish between a true ectopic kidney or congenital transdiaphragmatic hernia of a kidney if the renal artery is well displayed. With traumatic diaphragmatic rupture a kidney may be demonstrated in the thoracic cage. In a duplicated urinary tract one may identify both ureters and perform guided percutaneous puncture for antegrade pyelography. Horseshoe kidney and associated hydronephrosis, infection or calculus formation can be identified, but bowel gas may hamper visualization of the isthmus of the kidney. Ultrasound is the diagnostic method of choice in medullary cystic disease. In dominant adult polycystic disease ultrasound can identify cysts in the kidneys, spleen and pancreas, and one should search for infected cysts in patients with fever. Ultrasound-guided aspiration of the cyst can confirm the diagnosis.

Acute Renal Failure

Ultrasound is the primary screening procedure to differentiate urinary-tract outflow obstruction from parenchymal disease. However, normal ultrasound does not exclude urinary obstruction, because urinary dilatation can be missed with large calculi in the renal pelvis. All renal calculi cause acoustic shadowing, and the sonographer should search for associated dilatation.

Ultrasound cannot be used to differentiate between obstructive and non-obstructive urinary dilatation. Even minimal urinary dilatation should be further assessed by antegrade or retrograde pyelography.

Causes of obstruction that may be diagnosed with ultrasound are malignant neoplasms of the bladder, prostate, uterus, ovaries or rectum, retroperitoneal fibrosis, para-aortic lymph node metastases, primary retroperitoneal neoplasms, renal calculi and sloughed papillae.

In polyuric acute renal failure, urinary dilatation does not equate with obstruction, but if dilatation is marked, more invasive evaluation is indicated. Peripelvic cysts, vascular aneurysms, arteriovenous malformations, adult polycystic kidney disease and multicystic dysplastic disease must be distinguished from urinary tract dilatation. Progress after plastic

surgery on efferent urinary passages and hydronephrosis in pregnant women can be monitored. Ultrasound-guided nephrostomy is another important use. Percutaneous renal biopsy is essential for the initial diagnosis of renal parenchymal disease and progression of the disease can be monitored by ultrasound. Calcium deposition in the cortex or medulla has a characteristic appearance.

Renal Infection

Sonography is the initial screening technique used to evaluate suspected inflammatory disease. It is often normal with acute pyelonephritis, and diffuse or local renal inflammatory diseases have nonspecific sonographic appearances. An abscess cannot be distinguished from a tumour, but the combination of clinical presentation, the sonogram, and excretory urography or CT may support the diagnosis.

Pyonephrosis

Sonography is valuable in diagnosing parenchymal involvement. The clinical findings permit the differentiation between pyonephrosis and blood in the collecting system, and for a firm diagnosis aspiration of the collecting system may be performed.

Vascular Compromise

Venous tumour thrombus and acute renal vein thrombus can be diagnosed with real-time ultrasonography and Doppler ultrasound, combined with excretory urography. Renal arterial infarction and parenchymal haemorrhage, and sometimes renal artery thrombosis, can be demonstrated. In complete arterial occlusion no sonographic findings are seen. Enlargement of the renal vein may be due to tumour or arteriovenous shunting.

Perirenal Collections

Sonography is sensitive in detecting perirenal collections, but it is difficult to differentiate urinomas, lymphoceles, haematomas, abscesses or pancreatic pseudocysts with ultrasound alone. Clinical history and aspiration of fluid under ultrasound guidance is important in the differential diagnosis. With a perinephric abscess percutaneous drainage under ultrasound guidance can be performed. In a trauma patient sonography is highly accurate to detect renal fractures, contusions, intrarenal subcapsular haematomas and perirenal haematomas.

Renal Masses

Circumscribed renal masses larger than 0.5-1 cm can be diagnosed. Renal calucli larger than 0.5 cm can be visualized. Ultrasound is unsuitable for detection of carcinoma of the renal pelvis. When ultrasonography is technically suboptimal or the sonographic appearance of a cyst is equivocal, a CT or magnetic resonance study should be performed. Any atypical renal cyst should be punctured or studied further. Simple cysts, polycystic kidney disease and medullary cystic disease can be distinguished. Ultrasound is more specific than excretory urography for diagnosing polycystic kidney disease.

Benign and malignant tumours cannot be differentiated. Sonographically their appearances are non-specific, therefore clinical findings are very important to determine aetiology. The presence of an echodense intrarenal mass is not pathognomonic for angiomyolipoma, as renal cell carcinoma may present in the same way. The display of the renal vein and inferior vena cava is important in preoperative staging of renal cell carcinoma to determine resectability, but CT is superior to ultrasound in tumour staging. A solid mass in the kidney may also be a Wilms' tumour or nephroblastoma. Sonography of lymphomatous involvement of the kidney is not specific, but may be confirmed by gallium scanning.

Renal Transplants

A 3.5 or 5 MHz transducer is used. Renal anatomy, such as size and shape, and pathology can be well delineated. Sonography can diagnose obstruction, but when dilation of the collecting system is present, sonographic and radiologic antegrade pyelography is advocated.

Sonography is more sensitive than either excretory urography or radionuclide studies in detecting perirenal fluid collections such as lymphoceles and haematomas. However, sonographic appearance of fluid collections is nonspecific, and to reach a correct diagnosis under ultrasound guidance, percutaneous puncture and aspiration of fluid is desirable. Renal cysts and stones, abscesses and infarcts can be visualized and evaluated. Acute and chronic rejection phenomena, as well as infections, can be monitored. Pulsed Doppler duplex sonography provides an indicator of renal venous and arterial blood-flow patterns. The limitation is that minimal changes are undetectable or only poorly visualized.

Adrenal Ultrasonography

A 3.5 MHz or 5 MHz transducer is used. The normal adrenal gland is not imaged as a distinct structure. Ultrasound examination of the adrenal gland is technically difficult, and CT is the imaging procedure of choice for evaluation of adrenal glands. Sonography is preferred in children, pregnant women, thin adults, patients with known metastatic disease, and when CT is unavailable.

Ultrasonographic Signs of Adrenal Disease

A mass in the right adrenal area must be differentiated from a hepatic, renal or retrocaval lymph node mass, and normal structures such as the crura of the diaphragm, and the second portion of the duodenum. It is difficult to differentiate between adrenal masses and enlarged lymph nodes or other retroperitoneal masses. A mass in the left adrenal area must be differentiated from splenic, renal and pancreatic lesions, and normal structures such as the oesophagogastric junction, stomach, body of the pancreas, medial lobulation of the spleen, splenic vessels and the left renovascular bundle. Real-time scanning with water ingestion and Doppler techniques may help distinguish the normal bowel and vascular structures.

Adrenal Pathology

Sonography cannot distinguish between primary adrenal tumours, such as aldosteronoma, pheochromocytoma and neuroblastoma, and metastatic disease. The pattern

of adrenal metastases is nonspecific. It is useful in evaluating patients with known primary tumours for the progression of metastatic adrenal disease. The value to locate extra-adrenal pheochromocytoma is limited and it has no value in evaluating the chest for extra-abdominal pheochromocytoma. CT and fine needle biopsy are helpful in further characterizing lesions. Sonography is ineffective in examining patients with Cushing's disease, because of obesity, and it is difficult to distinguish adrenal hyperplasia secondary to pituitary malfunction from an adrenal adenoma.

Adrenal cysts and/or calcifications can be identified. Cysts may be secondary to haemorrhage or true cysts, such as retention cysts, cystic adenomas or angiomatous cysts. They must be distinguished from renal cysts, splenic cysts, hydronephrosis or pancreatic pseudocysts.

Ultrasound of the Aorta

Patient preparation is the same as with all abdominal examinations and sonography must also be scheduled before barium studies. The 3.5 MHz medium or long focus, or 5.0 MHz medium transducers are routinely used.

As a result of ageing, the aorta enlarges. Dilatation of the aorta is more often seen in men than women. The median diameter in the eight decade is $22.8 \text{ mm} \pm 2.8 \text{ mm}$ for men and $16.9 \text{ mm} \pm 2.5 \text{ mm}$ for women.

Pathology of the Aorta

Atherosclerosis manifests with plaque formation in the abdominal portion of the aorta and the major consequences are luminal obstruction and aneurysms.

Obstruction

In this condition the aortic diameter is normal and the thrombus may appear as a hyperechogenic intraluminal mass or as a normal anechoic vascular channel, in which case the diagnosis will only be confirmed with duplex Doppler. With real-time, prominent pulsation can be seen in the patent proximal aorta which is absent in the occluded aorta.

Aneurysm

Ultrasound has been reported to be 94-100% accurate in detecting abdominal aortic aneurysms. Failure to detect an aneurysm has been attributed to overlying bowel gas and confusion with para-aortic masses when older apparatus was used. The aneurysm should be measured. The anteroposterior (AP) diameter should be measured on both longitudinal and transverse scans but is more accurate on the axial plane. The best correlation between aneurysmal size and sonographic measurement occurs when measurements are taken from the leading echo of the anterior wall to the anterior echo of the spine. Change in size should be documented during follow-up examinations. It is important to detect whether an aortic aneurysm extends into the iliac arteries, and to delineate the relationship of the aneurysm to the renal arteries.

Rupture of the aortic aneurysm is dependent upon aneurysmal size and on the presence and location of a mural thrombus - the rupture normally occurs where thrombus is absent.

Because of patient instability ultrasound rarely plays a role in diagnosis of rupture but is useful in detecting a contained rupture.

Dissection

Sonography plays a role in the diagnosis of acute dissection. The intimal flap appears as an extralinear echo in the lumen.

Postoperative Ultrasound of the Aorta

Post-operative complications include haematomas, infection and false aneurysms demonstrated as sonolucent masses extrinsic to the grafts - while obstruction can be confirmed with duplex Doppler.

The Retroperitoneum

Sonographic demonstration of retroperitoneal structures is often hampered by bowel gas, bone and thick muscle or fatty layers. These impediments dictate a very flexible approach to the retroperitoneal space. Besides longitudinal and transverse scans, coronal scans with the patient in the decubitus or supine position will also allow visualization of the retroperitoneal space.

Signs of Retroperitoneal Disease

The most common sign is the presence of a mass, and by carefully demonstrating the boundaries of the mass as well as the way in which it displaces organs and vasculature one can often diagnose the organ of origin and, occasionally, also the retroperitoneal compartment involved. Masses can be further characterized with respect to their internal echo pattern.

Other signs of retroperitoneal disease are:

- Abnormal displacement of normal structure.
- Direct invasion of retroperitoneal organs.
- Assymetry of normal bilateral structures (this is especially true for tumours or inflammatory processes involving muscles of the retrofascial space).
- Loss of normal retroperitoneal detail - CT should be done to confirm the suspicion.

Retroperitoneal Pathology

Lymphadenopathy

The sonographic appearance is variable. Focal, discrete hypoechoic to anechoic masses are common, but a hypoechoic mantle surrounding the paravertebral vessels may also be seen.

Primary Neoplasms

Primary retroperitoneal neoplasms are uncommon and are mostly mesenchymal sarcomas.

The appearance of these tumours is variable and nonspecific, but by noting location, the presence of cystic areas of necrosis or calcification and correlating these findings with the patient's history, the examiner can suspect the diagnosis of retroperitoneal neoplastic disease. Sonography can be used to direct biopsies and monitor response to therapy.

Fluid Collections

Include haematomas, abscesses, urinomas and lymphoceles - all of which may have similar sonographic appearances. Ultrasound provides superior definition of the internal features and wall structure and accurately distinguishes cystic masses and fluid collections from solid abnormalities.

Retroperitoneal Fibrosis

May be idiopathic, secondary to drugs, retroperitoneal bleeding or infection, or due to an infiltrative tumour. Sonographic findings include the presence of a smooth-walled, hypoechoic to anechoic mantle that envelops the distal prevertebral vessels and may extend down to the sacral promontory. Sometimes retroperitoneal fibrosis may be indistinguishable from lymphoma, sarcoma or other malignancies. Retroperitoneal fibrosis may also resemble infection or haemorrhage. It may coexist with abdominal aortic aneurysms. Unilateral or bilateral hydronephrosis may be present - retrograde urograms will confirm such obstruction and ultrasound guidance can be used to place nephrostomy tubes.

Pitfalls in the Diagnosis of Retroperitoneal Disease

Aberrantly located normal organs like ptotic kidneys, horse-shoe or pelvic kidneys or a low-lying pancreas account for frequent errors as do aperistaltic bowel loops. Because many pathologic processes involving the retroperitoneal space may have a similar sonographic appearance, the correct diagnosis may only be possible after additional diagnostic or interventional procedures have been performed.

Pelvic Ultrasonography

Improved resolution real-time instrumentation now permits evaluation of much smaller structures (i.e. ovaries, seminal vesicles). A wide range of studies in the male patient has also evolved and is providing greater diagnostic capability. It should be remembered that in

addition to the male and female genitourinary tract the pelvis is formed by the tissues of the pelvic sidewall, and contains the large and the small bowel. Pathologic conditions involving these structures may also be present on pelvic sonography.

For examination of the pelvis a distended bladder is required. This could be obtained by oral intake of several glasses of water 30-40 minutes before examination or intravenous diuretics or retrograde filling of the bladder through a catheter. In some cases significant bladder filling is impossible, i.e. patients who have undergone cystectomy or have large pelvic masses.

The male pelvis is examined in three ways:

- Through a distended bladder using a real-time sector-scanning probe.
- By introducing a probe in the rectum and advancing it to the appropriate level.
- An endoscopic approach by a small rotational transducer mounted on a cystoscope.

The Urinary Bladder

A wide spectrum of pathology involving the bladder is demonstrable. Intravesical lesions are easily seen because of the natural contrast provided by urine. Included among these are:

- **Tumours:** Since sonography is capable of examining the entire periphery of the bladder, one sometimes encounters lesions that cannot be easily seen on cystoscopy. When these masses arise from the base of the bladder, there may be some confusion as to whether the source is the prostate or the bladder.

- **Calculi and clots:** Both appear as dependent echogenic structures that shift position rapidly as the patient's position shifts. They may be differentiated from each other by the acoustic shadowing accompanying stones, which are easily distinguished from the bladder-wall calcifications, i.e. Schistosomiasis.

- **Uretherocele.**

- **Diverticula.**

The Prostate

Sonography can provide an excellent estimate of the size of the gland as well as the seminal vesicles. However, attempts to differentiate prostatic cancer and benign hypertrophy have been less successful.

Ultrasonography of the Scrotum

Sonography is a rapid, non-invasive means for evaluating the scrotal contents. Testicular and extratesticular pathology can easily be distinguished. This distinction is

particularly important as most testicular masses are malignant while most extratesticular masses are benign. The scrotal ultrasound examination is performed using high-frequency real-time equipment and contact scanning, allowing optimal anatomic positioning of the scrotal contents and evaluating of a palpable mass. Indications for scrotal sonography include the evaluation of scrotal trauma, scrotal infections, acute scrotal pain, palpable scrotal masses, and follow-up evaluation of patients with previous scrotal infections, evaluation of patients with a prior history of testicular neoplasms, leukemia or lymphoma, and patients with chronic infertility syndromes.

Testicular Masses

Separating intratesticular from extratesticular pathology is the most valuable diagnostic information provided by scrotal sonography. Improved equipment and diagnostic skills allow this distinction to be made with $\pm 90\%$ accuracy. In appearance testicular neoplasms are indistinguishable from lesions such as abscesses, infarctions or haemorrhage. High frequency ultrasound can detect non-palpable primary lesions as small as 3 or 4 mm in size. It is not possible to distinguish ultrasonographically between benign and malignant masses therefore all intratesticular lesions must be considered potentially malignant until proven otherwise.

Extratesticular Lesions

The potential space between the two layers of the tunica vaginalis may be filled with accumulations of serous fluid, blood, infectious debris or urine. The most common fluid collections are hydroceles caused by trauma, infection, infarction and torsion. Haematoceles and pyoceles are less common but may have a similar ultrasound appearance.

Varicoceles, spermatoceles and epididymal cysts are easily distinguishable. Scrotal hernias are usually clinical obvious, however, the diagnosis may occasionally be in question. Ultrasound scanning of the scrotum and inguinal canal facilitates the diagnosis by identifying the small bowel or omentum in these areas.

The Acute Scrotum

The major causes of an acutely painful and swollen scrotum are torsion of the testis and acute epididymitis. The combined use of high-resolution sonography, Doppler studies and radionuclide scanning frequently allows the clinician to make this distinction. In testicular torsion ultrasonographic changes occur such as testicular and epididymal enlargement with decreased echogenicity, loss of spermatic cord Doppler findings, scrotal thickening and the appearance of a hydrocele. Decreased or absent flow is a specific Doppler finding. In epididymitis the bloodflow is increased and an enlarged hypoechoic epididymis associated with an otherwise normal testis is present. In testicular trauma with rupture of the testis, a non-homogenous appearance, with accompanying haematocele are the sonographic findings.

Penile Ultrasonography

It remains essential to differentiate between psychogenic impotence and organic impotence. Organic impotence may be neurogenic or vasculogenic. Ultrasonography is a non-invasive method of investigation using a 5 MHz linear scanner with a gel pad or 3.5 MHz

transducer with a waterbath. Proximal, middle and distal transverse images are obtained to evaluate intracavernous fibrotic areas which represent end-organ failure or organic impotence.

Vasculogenic impotence: The measurement of penile systolic pressure has been useful in the evaluation of male impotence. This is measured by using a small, digit-sized pneumatic cuff and a 10 MHz continuous-wave transducer for monitoring flow in a penile artery distal to the cuff. Reduced pelvic blood flow is usually associated with occlusive arterial disease affecting the lower extremity. In young potent males, the ratio of penile to brachial artery systolic pressure is greater than 0.8; a ratio less than 0.6 is consistent with penile arterial insufficiency. Because of the wide variability in penile systolic pressure among potent and impotent males, a multidisciplinary diagnostic approach to the problem of impotence is necessary.

Ultrasonography of Thyroid, Parathyroid, and Neck Masses

The use of high-resolution (5.0 MHz, 7.5 MHz and 10 MHz) real-time equipment has resulted in improved resolution in all small parts.

Thyroid

The indications for ultrasonography of the thyroid are almost always patients initially seen with a palpable nodule. Ultrasound is used to differentiate cystic from solid or complex lesions. There is no specific ultrasound characteristic to differentiate benign from malignant lesions. Where percutaneous aspirations/biopsy is required to establish a diagnosis it can be done with fine needle aspiration biopsy under ultrasound guidance, to select the correct site of sampling. In the thyroid a lesion as small as 3 to 4 mm can be detected.

Pathology

The diagnosis of thyroid pathology is based on clinical and laboratory studies because, for example, Graves' disease, acute and subacute thyroiditis and Riedel's struma cannot be distinguished sonographically because they all cause a diffuse enlargement.

Lesions

Cysts: The role of ultrasound is to detect and characterize thyroid nodules and to size and locate them for initial evaluation as well as for follow-up studies. About 20% of solitary thyroid nodules are cystic and cysts are almost uniformly benign. Some cysts have dense echoes that may be the result of haemorrhage.

There are no reliable ultrasonographic criteria to differentiate primary or secondary thyroid malignancy from benign tumours. The majority of fluid-filled areas within a nodule represent haemorrhagic or colloid degeneration within adenomas.

A thyroglossal duct remnant is an anteriorly located neck mass. Ultrasonographically it appears as a fluid-containing lesion with multiple bright internal echoes.

Salivary Glands

The role of ultrasound is to detect whether palpable neck masses are within the salivary glands or extrinsic within adjacent lymph nodes.

Extrathyroid Neck Masses

Branchial cleft cysts are usually solitary and located unilaterally and laterally. Although primarily cystic in appearance these lesions may present with low-level internal echoes, particularly if they have become infected. These cysts can be differentiated from cystic hygroma which will appear as a multicystic mass.

A branchial cleft cyst may be indistinguishable from a simple abscess laterally located in the neck. Chronic abscesses are very difficult to demonstrate since their indistinct margins blend with surrounding tissue. The role of ultrasound is to locate the area for percutaneous needle aspiration and follow-up examinations after treatment.

Adenopathy, either inflammatory or neoplastic cannot be distinguished from each other and appear as relatively anechoic well-circumscribed lateral neck masses.

Parathyroid

The diagnosis of hyperparathyroidism is based on clinical and laboratory studies. The role of ultrasound is to determine the site of enlarged glands in patients with the diagnosis of hyperparathyroidism.

The parathyroid echo pattern is similar to that of the thyroid and because of their size and texture they are not seen normally. Enlarged glands are relatively more anechoic. If parathyroid adenoma is within the thyroid gland, it typically has an echogenic margin, so that it can be distinguished from an adenomatous thyroid gland. However, it may be difficult if there are also thyroid abnormalities present.

Enlarged glands must be differentiated from enlarged lymph nodes, because lymph nodes are usually located more laterally. Sonography has resulted in the detection of 80-90% of enlarged glands in the neck because of the use of high-resolution real-time equipment. The mediastinum cannot be evaluated by sonography because of the bony thoracic cage and the lungs. If the sonographic examination of the neck is negative, other localizing studies such as scintigraphy, digital subtraction angiography and CT are indicated to search for ectopic and/or mediastinal glands.

In most cases all the glands are involved in hyperplasia. There are no characteristics to distinguish between adenoma, hyperplasia or carcinoma. A single enlarged gland favours the diagnosis of an adenoma. Although multiple adenomas can occur in cases of hyperparathyroidism, hyperplasia is still the commonest aetiology.

Ultrasound has been utilized to guide fine-needle aspiration biopsy of enlarged parathyroid glands.

Breast Ultrasound

The most important clinical use of breast ultrasound is still to differentiate cysts from solid masses. Needle aspiration of palpable masses is easy to perform and usually therapeutic as well as diagnostic. Ultrasound is also recommended for the evaluation of a patient with breast cysts so numerous as to make aspiration impractical and can be repeated as often as necessary. Breast ultrasound is a useful adjunct to mammography in the following clinical situations:

- When the parenchymal tissue is so dense that it limits mammographic examination
- When mammography of palpable masses has indeterminate features
- When mammographically detected masses, that are not palpable, have indeterminate features.

However, ultrasound's sensitivity and specificity in the detection of breast cancer are far lower than the figures reported for mammography.

The following examples show the limitations and poor results of ultrasound in the detection of breast cancer.

- Distinguishing benign from malignant masses - poor results.
- Inability to depict microcalcifications.
- Identification of solid lesions less than 1 cm in diameter - poor results.
- Fatty breasts - poor results.

The combined use of mammography and ultrasound has been shown to improve the detection rate for breast cancer.

Duplex Doppler or Duplex Sonography

Duplex Doppler, or duplex sonography, uses a combination of realtime ultrasound, providing anatomic information, and pulsed- or continuous wave Doppler ultrasound, providing blood-flow data.

Doppler Physics

The Doppler effect is caused by a change in frequency of a sound wave resulting from motion. The motion may be that of the wave source or wave receiver or in the case of a reflected wave the motion of the reflector. In medical application the ultrasound transducer which is both source and receiver of ultrasound, is stationary and the Doppler effect is generated by motion of the reflector - the red blood cells in circulation being the dominant reflector. If motion is towards the transducer, the echo frequency is greater than the frequency

of the transmitted sound wave and if motion is away from the transducer, the echo frequency is less than that of the transmitted sound wave.

The Doppler equation provides a quantitative relationship between the flow speed and the change in frequency.

$$f_D = (2 f v \cos(\alpha) \times V) / C = (f_D \text{ wave}) / 2f \cos(\alpha)$$

f_D is the Doppler shift frequency (difference between transmitted frequency and echo frequency) - in kHz cm/sec or m/sec.

f is the transmitted frequency - known.

V is the reflector speed - unknown.

α is the angle between reflector motion and transmitted pulse direction (fig. 1).

C is sound speed 1540 m/second - constant for soft tissues.

When the sound beam is projected along the same direction as blood flow, α is 0, and $\cos\alpha$ is 1. Where α is greater than 0, the detected Doppler frequency shift is reduced to the $\cos\alpha$ term which is still ± 1 as long as α is less than 25 degrees.

$$\cos 5 = 0.996$$

$$\cos 10 = 0.988$$

$$\cos 25 = 0.923$$

$$\cos 30 = 0.891$$

$$\cos 60 = 0.587$$

$$\cos 90 = 0.15$$

Therefore, where the beam is perpendicular to the flow direction - no Doppler shift is detected! In practice the transducer beam is usually oriented to make a 30-60 degree with the vessel lumen.

Continuous-Wave Doppler (CW)

CW Doppler detects velocity information along the entire length of the sound beam, and easily records the highest velocities within the beam. There is no simultaneous two-dimensional imaging as with pulsed-Doppler. Real-time imaging with CW Doppler is now available.

In a single housing two transducer crystals are mounted side by side. One transducer is continuously generating sound waves and the other is continuously receiving reflected sound waves. Signals returning from all depths are being analyzed. There is therefore no range resolution and it cannot localize flow-velocity information.

Colour Flow Mapping

Recent technology advances have introduced a new two-dimensional colour flow mapping system. The system basically uses pulsed-Doppler and performs analysis at multiple

points along each scan line of echodata. Flow information is then colour coded and displayed on a superimposed corresponding two-dimensional image.

Equipment

Duplex instruments are either mechanical array or phased array and the transducers either sector, convex or linear array.

Duplex Sonography of the Cerebrovascular system, of peripheral arteries and of lower-extremity venous systems, are briefly discussed.

Duplex Doppler of the Cerebrovascular System

Atherosclerosis of extracranial portions of arteries supplying the brain are far more common than atherosclerosis of intra-cranial arteries. The origin of $\pm 80\%$ of all cases of amaurosis fugax or TIAs can be traced to the carotid bifurcation.

Arteriography remains the "gold standard" for the detection of carotid atherosclerosis and is still imperative before undertaking endarterectomy. It is, however, a highly invasive procedure and carotid angiogram is not to be recommended without a high suspicion of identifying a significant and hopefully correctable lesion - this is where *duplex Doppler* plays a major role.

Real Time Imaging of Carotid Arteries

Although theoretically the carotid arteries seem ideal for real-time sonography, in practice, when applied to carotid occlusive disease, this technology proved to be less successful. Real-time imaging alone is inadequate to diagnose carotid stenoses - as the severity of occlusion increases the quality of the real-time scan decreases. The difficulty of distinguishing between normal and total occlusion is referred to in almost every real-time study. Furthermore the real-time differentiation of the internal carotid artery (ICA) and external carotid artery (ECA) is not reliable and becomes even more difficult when atherosclerosis is present.

However, the acoustic properties of blood and plaque may be to our advantage in situations in which good bloodflow is present. This provides an excellent contrast to plaque. Real-time ultrasound therefore seems best suited for the evaluation of plaque and not for diagnosing stenosis.

Using high-resolution real-time technology, atherosclerosis exhibits a number of rather specific features differentiating fibrofatty from calcific plaque. Although plaque ulceration may be demonstrated, a significant number of ulcerations are not recognized.

According to recent studies intraplaque haemorrhage is a possible cause for many ischaemic cerebral events. The real-time finding most often associated with intraplaque haemorrhage appears to be nonhomogeneity where the anechoic areas present the intraplaque haemorrhage.

Real-time technology is the only effective means of diagnosing extraluminal events, and it may prove far more useful than merely providing a roadmap for better Doppler localization.

Doppler Studies of Extracranial Carotid Arteries

Noninvasive Doppler studies of carotid arteries are divided into two categories, direct and indirect. Direct studies are aimed specifically at the carotid bifurcation, while indirect techniques are used to try and identify collateral pathways which developed because of carotid bifurcation, or ICA disease.

There are two major Doppler flow patterns encountered in the neck and throughout the body, namely, the low resistance diphasic wave pattern and the high resistance triphasic wave pattern.

The Doppler spectral analysis is merely a reflection of red blood cell velocity and the speed at which blood flows, is influenced by numerous factors:

- **Cardiac output:** Normally a rapid rise in blood cell velocity occurs throughout the body with each systolic contraction. This forward velocity then decreases or ceases altogether as diastole progresses.

- Almost as important as the cardiac output is the effect of the **distal arteriolar runoff.**

Low resistance vascular beds are generally those of blood-hungry organs such as the brain, the liver or the kidneys. Although differences exist, flow in all these low-resistance vessels follows a diphasic or low-resistance pattern (fig. 2) - a relatively slow rise with systole and gradual decrease as diastole progresses. Unique to the normal diphasic wave-form is the fact that flow never reaches zero, even at end diastole forward flow continues. The Doppler spectrum never returns to the baseline.

The Doppler pattern of high-resistance vessels is somewhat more complex. These vessels supply the vascular beds of muscular structures of the body. The aorta, subclavian and ileo-femoral artery systems are typical examples. Likewise the external carotid artery supplies the muscular structures of the face and exhibits a typical high resistance Doppler pattern. Flow in these arteries is always under considerable pressure - the blood flow has a much "snappier" quality than low-resistance arteries. Blood velocity rises sharply during systole and falls rapidly with cessation of the cardiac contraction. The normal high-resistance system is also quite elastic. The high arterial end pressure sets up a rebound phenomenon when blood flow actually reverses for a short time after systole. During the remainder of the cardiac cycle no forward flow occurs and the Doppler signal therefore remains on the baseline - resulting in a triphasic waveform (fig. 3). This distinction between low-resistance and high-resistance blood flow is of the utmost importance in the carotid systems.

Using Doppler alone the experienced operator should be able to distinguish the ICA from the ECA.

Out of the above discussions it is clear that duplex Doppler has greater diagnostic value than real-time imaging or Doppler studies alone.

Non-quantitative Doppler suffices in many areas in the body - stenosis may be less important for example, than flow direction or identification of inappropriate vascular resistance. However, precise quantification of carotid blood flow is required if any noninvasive test is to be successful.

Doppler is not particularly reliable in lesions which are less than 50% occluded.

In evaluating stenosis, the maximum systolic velocity or kHz shift is the single most important feature of the Doppler data (scanning angle usually 45-60 degrees).

Unfortunately variation is frequent. A 3 kHz or lower Doppler shift is common in the older atherosclerotic population, while a considerably higher kHz Doppler shift can still be normal for an apparently healthy young subject. Caffeine, tobacco and stress can also influence this peak systolic Doppler-shift.

In general, flow velocity is directly proportional to the degree of luminal narrowing and with increasing velocity, pronounced spectral broadening is encountered. Although this is the rule, abnormally high velocities and relatively clean Doppler traces have been seen in patients with high-grade stenoses. Conversely true, spectral broadening, filling the sonic window but without marked velocity increase should also be viewed with suspicion - low velocity is usually encountered in patients with poor cardiac output. In any atypical situation low flow, high flow, etc, the use of multiple Doppler criteria, particularly ratios like

Velocity ICA/Velocity CCA and ICA systole/ICA diastole

can be important.

Stenoses that narrow the lumen 75-90% are the most obvious lesions for Doppler examinations, and Doppler reaches its highest accuracy in this area. An increase in diastolic flow velocity beyond 4.5 kHz shift is a sign of stenosis greater than 80%. Again, the most typical abnormality is the markedly increased velocity at peak systole.

As the carotid lumen becomes stenosed beyond 90% flow velocity actually begins to decrease. These lesions may present difficulty in their diagnosis as their maximum flow velocities are often well within the normal range. In most cases, however, there will be an extremely distorted waveform often better heard than seen. Typically subtotal stenosis sounds very abnormal.

It should be emphasized that subtotal lesions are not static - if intervention is contemplated in patients with high-grade lesions, it should be carried out as soon as possible. Total occlusions are not surgical lesions.

Total occlusion is not often a straightforward diagnosis with large solid or calcified plaque filling the origin of the ICA and an absent Doppler trace. More typically externalized (high resistance) flow will be found throughout the CCA, but at the origin of the ICA a

normal anechoic lumen will be seen, but no Doppler flow will be found in spite of an exhaustive search.

In some cases the occlusion may begin distally to the origin of the ICA, thus exhibiting a patent ICA on real-time imaging but with a very unusual flow pattern - called "stump flow" probably due to blood merely sloshing back and forth in the stump lumen - making a "thudding" sound.

Further complicating the diagnosis of subtotal to total occlusion is the fact that as the ICA narrows, the ECA frequently begins to take on more low-resistance flow characteristics - probably the result of the opening of widespread ECA/ICA collaterals.

In order to determine if a vessel is truly the ECA, tapping on the temporal artery will show the "tapping" effect during diastole in the ECA Doppler flow pattern.

To help diagnose these collaterals the post-orbital Doppler technique, using a 4-5 MHz CW transducer is performed. In normal subjects flow direction is towards the transducer but when reversed post orbital flow is encountered, ECA collaterals have probably developed.

The Vertebral Artery

Two aspects of vertebral artery disease will be discussed: segmental stenosis and subclavian steal syndrome. Because stenoses distal to the origin of these vessels are extremely uncommon, we will limit our discussion to the area of the vertebral-subclavian junction.

The normal vertebral artery supplies a low-resistance vascular bed and produces a diphasic signal of lower velocity than found in the carotid artery of the same patient. In general, the diagnosis of vertebral artery stenosis should only be made when a focal area of increased peak velocity is found compared with flow elsewhere in the same vessel. When scanning between 45-75 peak systolic flow greater than 2 kHz indicated 50-99% occlusion.

Duplex Doppler is very helpful in the diagnosis of subclavian steal syndrome. In this situation a narrowing or occlusion of the proximal subclavian artery blocks the normal blood supply to the arm and the vertebral artery serves as a collateral pathway around the stenosis and flow in the vertebral artery is therefore reversed. A Doppler tracing with an optimum angle 45-60 must be used even if it means sampling from between vertebral bones. Demonstration of true flow reversal from any portion of the vertebral artery confirms the diagnosis.

Duplex Sonography of Peripheral Arteries

High-resolution real-time equipment with 4-10 MHz transducers with pulsed Doppler is required.

In the peripheral arterial tree, focal atherosclerotic lesions tend to develop in areas that are most prone to constant endothelial injury such as bifurcation or areas of posterior fixation - like the mid/distal superficial femoral artery in the region of Hunter's canal.

Before beginning any duplex examination of the legs careful attention should be given to the clinical history and physical findings. A complete evaluation of the arterial tree between aortic bifurcation and calf can be extremely time-consuming and a more directed evaluation is advisable.

The common femoral - superficial femoral - and popliteal arteries all have marked diphasic Doppler waveforms, while the profunda appears considerably more dampened and less triphasic - probably because the profunda immediately supplies a large vascular bed.

Signs of stenosis in peripheral arteries are:

- Markedly increased systolic velocity.
- Marked spectral broadening.

Auxilliary findings in stenosis are:

- Dampened waveforms distal to the stenosis, and
- Distortion of the typical triphasic waveform including:
 - Loss of the negative component - due to decreased vessel elasticity.
 - Flow throughout the diastole - due to peripheral vasodilatation.

Vascular Laboratory Equipment

The measurement of segmental systolic blood pressures in the lower extremities requires pneumatic cuffs of appropriate size, a manometer and a means for detecting distal flow. Cuff width is an important consideration in measurement of lower-limb blood-pressure. To minimize cuff artifact the cuff width should be at least 50% greater than the diameter of the limb.

Indirect Measurement of Arterial Pressure

The systolic pressure measured at the ankle is normally higher than that in the upper arm. In order to keep blood moving in the proper direction, however, the diastolic and mean pressures gradually decrease as the pulse wave moves distally.

Diastolic pressure in the lower limb is reduced only in the presence of severe proximal stenosis but the peak systolic pressure decreases with lesser degrees of disease. The term *critical stenosis* has been used to describe the degree of narrowing that produces a drop in distal pressure or flow. In the resting state distal pressure is reduced by stenosis that decreases luminal diameter by 50% or more. Blood pressure and flow are not necessarily altered to the same extent by arterial occlusive disease.

Ankle Pressure and Ankle Pressure Index

Measurement of ankle systolic pressure is the single most valuable test for assessing the arterial circulation in the lower limb.

Post-tibial and dorsalis pedis arteries are usually most convenient.

It is important to recognize that the level of pressure measurement is determined by cuff placement and not by the site of Doppler flow detection.

Since ankle systolic pressure varies with the central aortic pressure, it is desirable to compare each ankle pressure measurement with brachial pressure measurement, which is essentially equal to central aortic pressure assuming subclavian and axillary arteries are not obstructed. The ratio of ankle systolic pressure to brachial systolic pressure, or ankle pressure index, is always greater than 1 (mean value of 1.11 ± 0.10). In general limbs with single-level occlusions have indices greater than 0.5 and limbs with lesions at multiple levels have indices less than 0.5 and ankle pressure index also correlates with the degree of functional disability.

Segmental Pressures

Ankle pressure index cannot determine the location of proximal arterial lesions. This information may be obtained by measuring systolic pressure at various levels. Four pneumatic cuffs 11 cm wide, 83 cm long with 41 cm long inflatable bladders are used on each leg. The cuffs are applied at high thigh (HT), above knee (AK), below knee (BK) and ankle levels and systolic pressures measured at each level using the Doppler technique - An 8-10 MHz CW Doppler probe is placed over post-tibial or dorsalis pedis arteries.

The difference in systolic pressure between any two adjacent levels in the leg should be less than 20 mm Hg in normal individuals. Higher gradients indicate significant occlusive disease in the intervening arterial segment. HT-AK gradient reflects superficial femoral disease, AK-BK gradient reflects popliteal disease and BK-ankle gradient reflects disease in the tibial or peroneal arteries.

Exercise and Reactive Hyperaemia Tests

Exercise and reactive hyperaemia both increase limb blood flow by causing vasodilation. In limbs with normal arteries the increased flow causes little or no drop in ankle systolic pressures, while in limbs with occlusive lesions blood is diverted through high resistance collateral pathways and therefore pressure gradients which are minimal at rest may be accentuated with increased flow rates. Thus stress testing provides a method for detecting less severe degrees of arterial disease.

Summary of Lower-Extremity Examination

- Measurement of ankle pressure (post-tibial or dorsalis pedis) and brachial pressure at rest.
- Calculation of ankle pressure indices.

- Segmental pressure gradients if ankle pressures are abnormal.
- Duplex Doppler examination of femoral artery and bifurcation.
- Treadmill exercise or hyperaemia testing with repeat common femoral artery Doppler waveforms and serial ankle pressure measurements for less severe arterial disease.
- Toe pressure - to identify obstructive disease involving pedal arch and digital arteries.
- Penile pressure - to evaluate male impotence - see pelvic ultrasound.

Aneurysms

Aneurysms most commonly affect the abdominal aorta and popliteal artery. Although uncommon, aneurysms may also occur in the iliac and common femoral arteries. Those occurring in the iliac arteries are usually the most difficult to diagnose because of their deep location. Aortic, femoral and popliteal aneurysms are easily recognized by sonography which has been the recommended modality even before duplex Doppler was available.

Iatrogenic/Traumatic Vascular Lesions

Arterial bypass grafts, haemodialysis shunts (AV fistulae) and pseudoaneurysms are amenable to evaluation with high-resolution duplex sonography because of their superficial location. Although many grafts are palpable, a consultation with the vascular surgeon should be sought before performing the duplex evaluation. Knowledge of the postoperative vascular anatomy will greatly shorten the examination time and eliminate confusion.

Femoropopliteal bypass grafts are most frequently evaluated. The anatomy and material used, whether autogenous (saphenous vein) or synthetic prosthesis should be determined. Autogenous grafts are usually quite simple to evaluate, provided one does not apply too much pressure on the transducer.

Examination of synthetic grafts are more difficult to evaluate as this material may cause too much attenuation, thus degrading the quality of the examination.

The diagnosis of graft stenosis is made on the same signs as elsewhere in the body and is almost entirely dependent on Doppler, because on the real-time examination a thrombus often is totally anechoic instead of hyperechoic.

Haemodialysis shunts are also easily evaluated using Doppler sonography.

Duplex Doppler is particularly useful in the examination of palpable masses that occasionally develop around graft sites, vascular anastomoses, or arteriogram and IV injection puncture wounds. The differentiation between infection around the shunt and intrinsic ectasia and pseudoaneurysm should be easy.

Congenital arteriovenous malformations represent abnormal communications between a peripheral artery and vein and duplex sonography is an excellent screening modality in suspected patients. The real-time findings alone of a group of serpiginous cystic spaces are not diagnostic but should be supported by Doppler findings of increased arterial inflow and pulsatile venous outflow.

Duplex Sonography of the Venous System of the Lower Extremity

Basic knowledge of the deep venous anatomy of the lower extremity is mandatory in both performing and interpreting these ultrasound studies.

Ultrasound demonstrates both arteries and veins as adjacent, tubular branching structures and it is possible to distinguish between these vessels by their anatomic relationships and by various compression manoeuvres using duplex Doppler. By placing the sample volume centrally within the vascular lumen, a normal vein will show continuous low-velocity flow.

Technique of Lower Extremity Venous Sonography

A 5.0 MHz, 7.5 MHz or 10 MHz transducer is used. Doppler techniques enable immediate differentiation between arteries and veins and document vascular patency or occlusion.

Venous structures that can be examined sonographically include the common femoral vein, the superficial femoral vein (proximal and mid thigh), the popliteal vein and whenever possible the upper trunks of the calf veins.

Ultrasound Findings in Deep Venous Thrombosis (DVT)

Using real-time imaging blood flow can be demonstrated within a patent lumen and a discreet soft tissue mass within the lumen indicates a thrombus. Thrombi may show variable degrees of echogenicity. Potential pitfalls exist in using real-time alone: low-level intraluminal echoes may be the result of slow-flowing blood, which mimics thrombus. Conversely, the absence of echogenic material within a vascular lumen does not exclude the presence of a clot - because a fresh clot may appear virtually anechoic.

Consequently, various manoeuvres such as vascular compression and especially duplex Doppler have become an important part of the ultrasound diagnosis of DVT. Diseased vessels will be noncompressible, whereas a normal venous lumen is easily obliterated with gentle external pressure. The vein is noncompressible only in the abductor canal. Duplex Doppler is very useful for confirmation of either patency or occlusion of the distal external iliac veins, common and superficial femoral veins, popliteal veins and sometimes the trifurcation trunks of the major calf veins. Documentation of absent flow within a vein is usually sufficient to diagnose occlusion and other manoeuvres are then necessary.

Chapter 1.6: Chemical Pathology Investigations

H Vermaak

Introduction

Indications

Biochemical tests are used in diagnosis, monitoring patients' progress, screening for disease and for prognosis. The results of some biochemical tests provide specific diagnostic information but, in many instances, biochemical changes reflect pathological processes which are common to a number of diseases.

Interpretation of Results

When the result is obtained, the following questions arise:

- Is it normal?
- Is it significantly different from previous results?
- Is it consistent with clinical findings?

Is it Normal?

The normal range (or reference range) is obtained from measurements of a representative sample of sufficient size. This range is calculated by taking the mean \pm 2 standard deviations. Approximately 95% of the values in the population sample will be within this range. Numerous factors may influence this range, i.e.:

- **preanalytical:** fasting, drugs, alcohol consumption, posture, age, sex, race, pregnancy, time of day, exercise, physical state.
- **analytical factors:** methods, instruments, reagents, calibrants, techniques.

Normal value is a misnomer since a population sample may not be normal, i.e. cholesterol levels in subjects with a westernized lifestyle. Reference ranges are more appropriate.

Is It Significantly Different From a Previous Result?

This depends upon the precision of the assay itself and the natural biological variation. Whatever the biological variation, it can be shown statistically that if two measurements of a particular analyte differ by more than 2.8 times the standard deviation of the method there is a 95% probability that this is significantly different from the previous result.

Is It Consistent with Clinical Findings?

If the result is consistent with clinical findings, it is evidence in favour of the clinical diagnosis. If not, the explanation must be sought, i.e. there may have been preanalytical variables present which have invalidated the result.

Validity of Laboratory Tests

In using the result of a test, it is important to know how reliable the test is and how suitable it is for its intended purpose. These characteristics are described by its (clinical) specificity and (clinical) sensitivity. These terms should not be confused with analytical specificity which defines the degree of interference by other substances in the assay procedure. Analytical sensitivity refers to the minimum concentration which can be reliably determined. Clinical sensitivity is a measure of the incidence of positive results in patients known to have a condition, i.e. "true positives" (TP). Specificity is a measure of the incidence of negative results in persons known to be free of a disease, i.e. "true negatives" (TN).

A specificity of 90% implies that 10% of healthy people would be classified as having the disease on the basis of the test result; 10% would have a false positive result. The formula for calculating specificity is as follows:

$$\text{Specificity} = (\text{TN} \times 100) / (\text{all without disease} \times (\text{FP}/\text{TN}))$$

A sensitivity of 90% implies that only 90% of patients known to have the disease will be diagnosed as having it on the basis of that test alone; ten percent will be false negatives (FN). The formula for calculating sensitivity is as follows:

$$\text{Sensitivity} = (\text{TP} \times 100) / (\text{all with disease} \times (\text{TP}/\text{FN}))$$

The predictive value of a positive test defines the percentage of positive results that are true positives. The incidence of a disease has a pronounced effect on the predictive value, i.e. in a coronary care unit, the incidence of coronary heart disease is higher than in the general population, and the serum CK level will have a higher predictive value in that group than in the general population.

$$\text{Predictive value} = (\text{True positive} \times 100) / (\text{True positive}/\text{False positive})$$

Sodium

Reference Ranges: 136-146 mmol/L

Physiology

Na⁺ is the predominant cation in the extracellular compartment (ECF) and with its associated anions (Cl⁻ and HCO₃⁻) contribute 90 percent or more to the measured plasma osmolality. Total body Na (TB Na⁺) therefore determines the size of the ECF. True hyponatraemia is characterized by a low ECF osmolality and with a low extracellular Na⁺:H₂O ratio. It can be associated with either an increased TB Na⁺ (oedematous) normal

TB Na⁺ (isovolaemic) or low TB Na⁺ (hypovolaemic state). Hypernatraemia occurs when the extracellular Na⁺:water ratio is greater than normal and can be associated with an increased TB Na⁺ (hypervolaemia), normal TB Na⁺ (isovolaemia) or low TB Na⁺ (hypovolaemia). The therapy is determined by the TB Na⁺, i.e. diuretics for hyponatraemia with raised TB Na⁺ or saline for hyponatraemia with lowered TB Na⁺.

Interpretation

Hyponatraemia

Hypovolaemia (Lowered TB Na⁺)

- Renal loss: Renal tubular acidosis, salt losing nephritis, diuretic therapy, Addison's, acute tubular necrosis (polyuric phase).
- Extrarenal loss: Gastro-intestinal tract - vomiting, diarrhoea; respiratory tract - hyperventilation; skin-bruns, excessive sweating.

Isovolaemia (Normal TB Na⁺)

- Chronic water excess: Syndrome of inappropriate ADH secretion, hypocortisolism, hypothyroidism, acute and chronic renal failure, diuretics, drugs stimulating ADH secretion.
- Acute water excess: Postoperative, transurethral resection of prostate, stress.

Hypervolaemia (Elevated TB Na⁺)

- Extrarenal loss: Cirrhosis, CCF.
- Renal loss: Nephrotic syndrome.

Hypernatraemia

Hypovolaemia (Lowered TB Na⁺)

- Renal loss of hyponatraemic fluid: Osmotic diuresis - glucose (hyperglycaemia), urea (postobstructive) and post ATN (diuretic phase).
- Extrarenal loss of hyponatraemic fluid: Perspiration, vomiting, diarrhoea, dialysis.

Isovolaemia (Normal TB Na⁺)

Potential loss of "pure" water.

- Renal loss: Diabetes insipidus (central and nephrogenic)
- Extrarenal loss: Inadequate water intake - unconsciousness

Hypervolaemia (Elevated TB Na+)

- Oral: salt overload
- Parenteral: Hypertonic NaCl or sodium bicarbonate
- Mineralocorticoid excess: Conn's syndrome and iatrogenic.

Potassium

Reference Ranges: 3.5-5.0 mmol/L

Physiology

Potassium is the predominant intracellular cation which counterbalances the extracellular osmotic activity of Na⁺. Only 2% of total body K is present in the ECF, but is physiologically important in determining neural, muscular and cardiac activity together with ECF Ca⁺⁺ and Mg⁺⁺. A plasma or serum K⁺ < 2.0 mmol/L can be associated with muscle weakness and cardiac arrhythmias; > 7.0 mmol/L is lifethreatening; > 8.5 cardiac arrest or respiratory paralysis occurs.

Interpretation

Hypokalaemia

Intracellular Redistribution

Insulin, adrenaline, aldosterone, alkalosis, beta2 stimulants, i.e. salbutamol.

Extrarenal Loss

Associated with low plasma bicarbonate: Respiratory alkalosis, renal tubular acidosis, implantation of ureters to colon diuretic therapy.

- Associated with high plasma bicarbonate: Mineralocorticoid excess - Conn's syndrome, secondary hyperaldosteronism, iatrogenic, Bartter's syndrome, metabolic alkalosis.

Decreased Intake

Chronic alcoholism and anorexia nervosa.

Hyperkalaemia

Extracellular Redistribution

- Associated with normal bicarbonate: insulin deficiency, tissue necrosis, i.e. burns, crush injuries, hypertonicity, familial periodic paralysis (rare).

- Associated with low bicarbonate: ketoacidosis, lactic acidosis and renal failure.

Decreased Excretion

Mineralocorticoid deficiency, acute renal failure, severe chronic renal failure.

Artefactual

In vitro haemolysis, long delay in separation of red cells from plasma, thrombocytosis and leukocytosis.

Chlorides

Reference Ranges: 96-108 mmol/L

Physiology

Together with Na⁺ it plays an important role in ECF osmolality and in the maintenance of acid-base balance. Cl⁻ retention results in acidosis and loss in alkalosis. The control is closely related to that of Na⁺.

Interpretation

Hyperchloraemia

- Associated with elevated serum Na⁺
- Hyperchloraemic metabolic acidosis (normal anion gap acidosis): Diarrhoea, renal tubular acidosis, early uraemic acidosis, carbonic dehydratase inhibitors, ureterosigmoidostomy, HCl, NH₄Cl therapy, primary hyperparathyroidism
- Respiratory alkalosis

Hypochloraemia

- Related to hyponatraemia
- Metabolic alkalosis, i.e. Addison's, vomiting
- Respiratory acidosis
- Chloride loss: vomiting and diarrhoea

Bicarbonate

Reference Ranges: 21-28 mmol/L

Physiology

TCO₂ is an estimate of the sum of serum bicarbonate, carbonic acid and dissolved CO₂. Only a small quantity comes from dissolved CO₂ and carbonic acid. Actual bicarbonate is done on arterial blood and is either calculated from the Henderson-Hasselbalch equation or determined with ion-selective electrodes by blood-gas analyzers. It represents whole blood bicarbonate concentration as it is found in the patient. Standard bicarbonate measures the bicarbonate under standardized conditions of 37 °C and PCO₂ of 40 mm Hg (5.32 kPa). It reflects the bicarbonate concentration as if the lungs were normal. Therefore, in a patient with a mixed respiratory and metabolic acidosis, the standard bicarbonate reflects the metabolic component.

Interpretation

Increased

Compensated respiratory acidosis

Primary metabolic alkalosis

- Associated with urine chloride < 10 mmol/L: Indicates volume depletion: vomiting, diarrhoea, gastric suction, chloride diarrhoea, previous diuretic therapy.

- Associated with urine chloride > 20 mmol/L: Indicates volume expansion - mineralocorticoid excess, current diuretic therapy.

Decreased

Compensated respiratory alkalosis

Primary metabolic acidosis

- Normal anion gap acidosis - tubular acidosis, early uraemic acidosis, NH₄Cl ingestion/therapy, ureterosigmoidostomy

- Increased anion gap acidosis - Uraemia, lactic acidosis, ketoacidosis, intoxications.

Anion Gap

The anion gap is calculated from (Na⁺ + K⁺) - (Cl⁻ + bicarbonate⁻). The most useful application of the anion gap is to categorize metabolic acidosis, i.e.:

- High anion gap acidosis: Renal failure, lactic acidosis, ketoacidosis, intoxications (methanol, ethanol, salicylates)

- Normal anion gap acidosis: Renal tubular acidosis, diarrhoea, aldosterone deficiency, carbonic dehydratase inhibitors, treated diabetic ketoacidosis.

Urea

Reference Ranges: 1.8-6.4 mmol/L (infant/child)
2.5-6.4 mmol/L (adults)
2.9-7.5 mmol/L (elderly > 60 y)

Physiology

Urea, an end product of protein metabolism, varies widely with dietary intake of protein, liver production and renal excretion. Tubular reabsorption varies inversely with rate of urine flow which makes it less effective in determining the GFR than creatinine.

Interpretation

Increased

- Levels < 10 mmol/L: Early impairment of GFR, high protein intake (diet, GIT bleeding)
- Levels 10-20 mmol/L: Decreased GFR - prerenal or renal impairment
- Levels > 20 mmol/L: Renal impairment

Decreased

Decreased protein intake, liver failure, protein malabsorption, nephrotic syndrome with normal/near normal GFR.

Drug Effects on Laboratory Results

Elevated by nephrotoxic drugs, i.e. antibiotics, methyldopa, INH, propranolol, indomethazine.

Creatinine

Reference Ranges: 18-35 h mmol/L (infant)
17-62 mmol/L (child)
44-88 mmol/L (adolescent)
53-106 mmol/L (female adults)
71-133 mmol/L (male adults)

Physiology

Muscle ATP levels are maintained by phosphocreatine of which a proportion spontaneously forms creatinine. Creatinine levels are related to the mass of working muscle

and renal excretion. Unlike urea there is no tubular reabsorption although a small amount is secreted by the tubules. This does not lead to an overestimation of the GFR since the method used for measuring blood creatinine tends to overestimate the creatinine, which offsets the underestimation that would have otherwise occurred. With severe renal failure, creatinine clearance overestimates the GFR because of GIT secretion. Because of the non-specificity of the analytical reaction many substances, including common ones, such as ascorbic acid, acetone, acetoacetate, pyruvate, glucose, uric acid, barbiturates and the cephalosporin antibiotics may cause falsely-elevated creatinine levels. Creatinine may also be falsely lowered by high serum bilirubin concentrations. This nonspecificity causes serum creatinine determinations to be least useful in detecting mild abnormalities in GFR.

Interpretation

Elevated Levels

Kidney Related Causes

- Intrinsic renal diseases - acute and chronic renal failure
- Postrenal obstruction - urolithiasis, urethra stenoses, prostate hypertrophy.

Non-Kidney Related Causes

Hyperthyroidism, excessive growth hormone secretion - acromegaly, gigantism.

Decreased Levels

Physiological

Pregnancy, especially first and second trimester.

Decreased Muscle Mass

Elderly, paralysis, wasting diseases, dystrophias.

Urea/Creatinine Ratio

Normal Ratio: 40:1 in SI units

ŠPhysiology

In chronic renal failure the ratio remains unchanged because of the simultaneous increase in serum urea and creatinine levels with simple reduction of GFR. Prerenal and postrenal factors tend to increase the ratio because of the increased reabsorption of urea under conditions in which there is a decreased flow rate.

Interpretation

Table 1.6.1. Causes of abnormal serum urea to creatinine ratio

| Increased | Decreased |
|---------------------------|----------------------|
| High protein intake | Low protein intake |
| Gastrointestinal bleeding | Dialysis |
| Hypercatabolic state | Muscle wasting |
| Dehydration | Amputation |
| Urinary stasis | Severe liver disease |

Creatinine Clearance

Reference Ranges: 97-137 mL/min/1.73 m² (males)
88-128 mL/min/1.73 m² (females)†

In children, the clearance should be related to the body surface and, if this is done values similar to those in adults are found.

Slight renal failure: 52-62 mL/min/1.73 m²
Mild renal failure: 42-52 mL/min/1.73 m²
Moderate renal failure: 28-42 mL/min/1.73 m²
Marked renal failure: < 28 mL/min/1.73 m²

Pathophysiology

Creatinine clearance refers to the volume of plasma which could theoretically be completely cleared of creatinine per minute.

$$\text{CCr (mL/min)} = (\text{UrCr} \times \text{Ur vol (mL)}) / \text{Plasma Cr} \times \text{collection period (min)}$$

Theoretically clearance tests should be more sensitive than plasma measurements, however, the following sources of imprecision cast doubt on this notion:

- Inaccuracy of urine collection - can be as high as 30% in large series
- Inaccurate measurements of urine and serum creatinine. These inaccuracies are additive so that a fault of 30% under less ideal conditions is not uncommon.

Interpretation

Elevated Clearance

- Pregnancy
- High protein diet

- High cardiac output
- Hypercatabolic states
- Carbon-monoxide poisoning

Decreased Clearance

Decreased renal blood flow: Shock, haemorrhage, dehydration, congestive heart failure.

Intrinsic renal disease, glomerulonephritis, nephrotic syndrome, pyelonephritis, acute tubular necrosis, post renal obstruction.

Miscellaneous: Multiple myeloma, malaria, eclampsia, pre-eclampsia, hepatic failure, chronic obstructive lung disease.

Uric Acid

Reference Ranges: 0.27-0.48 mmol/L (males)
0.18-0.38 mmol/L (females)

Physiology

Uric acid, an end product of nucleoprotein metabolism, is excreted by the kidney. Purine rich diet (liver, kidney) and an increased nucleoprotein catabolism (chemotherapy, psoriasis) may increase uric acid. Gout, a hereditary metabolic defect, may lead to an overproduction, impaired renal excretion, or both. A sharp rise in serum (urate) is often not demonstrable, nor is plasma (urate) the sole predictive factor.

Interpretation

Elevated Levels

- Increased production: Increased tissue breakdown: tissue damage due to trauma, during acute starvation and chemotherapy; rapidly growing malignant tissue, i.e. leukemias, lymphomas and polycythemias.

- Decreased excretion: glomerular acidosis, low doses of salicylates, thiazide diuretics.

Decreased Levels

- Wilson's disease
- Syndrome of inappropriate ADH secretion
- Certain malignancies: Hodgkin's disease.

Calcium Serum

Reference Ranges:

| | | |
|--------------------|---------------|-------------------------|
| Total Ca: | Child: | 2.2-2.70 mmol/L |
| | Adult: | 2.2-2.55 mmol/L |
| Ionized Ca: | Adult: | 1.12-1.23 mmol/L |

Physiology

Approximately 45% of total Ca is bound to plasma proteins, especially albumin. 45% is in the ionized (physiologically active) form. Parathyroid hormone increase Ca and is regulated by a negative feedback from Ca. Calcitonin decreases Ca. 1,25 dihydroxycholecalciferol increases Ca absorption from the GIT. 99% of Ca is in bone, the 1% of extraosseous fraction is of great importance because of its effect on neuromuscular excitability and on cardiac muscle.

Interpretation

Elevated

- Hypercalcaemia with hypophosphataemia: Primary, tertiary and ectopic parathyroid hormone production.
- Hypercalcaemia with hyperphosphataemia: Vitamin D excess, sarcoidosis, bony metastases, severe hyperthyroidism.
- Hypercalcaemia with normal phosphate: Exclude artefactual hypercalcaemia due to prolonged venous stasis.

Decreased

Secondary hyperparathyroidism: Reduced dietary intake of Vitamin D, i.e. malnutrition; impaired absorption of Vitamin D, i.e. steatorrhoea; impaired metabolism of Vitamin D, i.e. renal disease; increased inactivation of Vitamin D due to anticonvulsant therapy.

Biochemical Tests to Investigate Ca Disorders

- **Serum total or ionized Ca, phosphate, albumin:** Correction factor for albumin concentrations for each 1 g/L a patient's albumin is below 40 g/L add 0.02 mmol/L to the total calcium and vice versa.
- **Serum alkaline phosphatase (ALP):** A normal ALP is usual in uncomplicated primary hyperparathyroidism.
- **Parathyroid hormone (PTH):** Primary hyperparathyroidism may be associated with increased or normal PTH levels. Renal failure is associated with increased PTH levels which

could be due to secondary (appropriate) or tertiary (inappropriate) hyperparathyroidism. Increased circulating levels of PTH may be present in a small number of patients with malignant hypercalcaemia.

- **Steroid suppression test:** It differentiates hypercalcaemia caused by primary or tertiary hyperparathyroidism from any other cause. Large doses of Cortisone suppress hypercalcaemia caused by non-parathyroidhormone disorders. It is more discriminatory when serum Ca levels exceed 3.0 mmol/L. Since steroids may cause water retention, Ca levels should be carefully adjusted according to changes in albumin levels. False positives have been recorded in some cases of advanced malignancies which do not usually cause diagnostic difficulties.

- **Urinary calcium excretion:** With normal renal function, total Ca excretion is less than 7.5 mmol/24 h. Hypercalciuria is of little value in the differential diagnosis, since hypercalcaemia by any cause will result in an increased Ca excretion by the kidneys.

- **Urinary phosphate excretion:** Theoretically, this should be a useful test because of the phosphaturic effect of PTH. The diagnostic specificity, however, is low since hypercalcaemia, *per se*, increases renal phosphate excretion. Dietary effects and inappropriate reference ranges further hampers its usefulness.

- **Urinary cyclic AMP:** AMP is the second messenger of PTH in the renal tubular cells and the calculation of the nephrogenic fraction has been found to provide useful diagnostic information. Relatively few laboratories offer this test.

- **Urinary osteocalcin:** This results from the osteoclastic effect of PTH on bone and does not have the disadvantages of hydroxyproline and hydroxylysine which requires special dietary precautions (gelatine-free diets).

- **Plasma urea:** Since prolonged hypercalcaemia may result in renal damage a serum urea or creatinine is indicated. Advanced renal failure will lead to hypocalcaemia and hyperphosphataemia which may obscure the typical findings of primary hyperparathyroidism.

- **Acid-base disturbance:** PTH suppresses the regeneration of bicarbonate and the renal excretion of hydrogenium which leads to a renal tubular acidosis with hyperchloraemia and a low serum bicarbonate. These changes are not always detectable.

Phosphate

**Reference Ranges: 1.5-2.8 mmol/L (children)
0.7-1.2 mmol/L (adults)**

Physiology

The concentration of circulating inorganic phosphate is decreased by PTH through its dominant phosphaturic effect on the renal tubular cells, which exceeds the stimulation of phosphate uptake from the GIT by PTH. Vitamin D increases the absorption and reabsorption by the GIT and kidney, respectively, which leads to raised Ca and phosphate levels. There

is often a slight fall in phosphate concentration after a carbohydrate meal due to an insulin mediated intracellular shift. A fasting state is therefore required when specimens are collected. Prolonged standing or haemolysis will increase serum phosphate levels because of the high intracellular concentration. Approximately 85% of total body phosphate is present in the skeleton.

Interpretation

Elevated Levels

- Artefact: In vitro haemolysis or prolonged contact of plasma with erythrocytes.
- Redistribution from intracellular to extracellular compartment: Insulin deficiency, starvation.
- Release from bone: Malignancies.
- Increased intake: Diet, excess vitamin D, inappropriate IV administration.
- Decreased excretion: Renal failure, hypoparathyroidism, acromegaly.

Decreased Levels

- Decreased intake: Vomiting, malabsorption; complexing with Ca or antacid therapy.
- Extracellular to intracellular redistribution: High carbohydrate diet, alkalosis, treatment of diabetic ketoacidosis.
- Increased excretion: Excess PTH, renal phosphate leak, diuretics, hypopituitarism with growth hormone deficiency.

Magnesium

Reference Ranges: 0.75-1.25 mmol/L

Physiology

50% is present in the skeleton, less than 1% is found in the extracellular fluid where it plays an important role in neuromuscular and cardiac excitability. The rest of the magnesium is found in the soft tissues. Plasma levels may not necessarily reflect magnesium deficiency, and when it is depressed it may be associated with tetany, weakness, disorientation and somnolence.

Interpretation

Elevated Levels

- Increased intake: Oral, parenteral.
- Decreased excretion: Acute and chronic renal failure.

Decreased Levels

- Decreased intake: Starvation, malabsorption, hyperalimentation and prolonged gastric secretion.
- Renal losses: Alcoholism, diuretic therapy, osmotic diuresis, hypercalcaemia.
- Extrarenal losses: Prolonged diarrhoea, laxative abuse, loss from fistula.

Enzymes

Cardiac Enzymes

CK, AST and LD are also present in other tissues and thus not specific for heart tissue.

Creatine Kinase (CK, previously CPK)

Reference Ranges: 30-110 IU/L at 37 °C

Physiology

Most abundant in heart, skeletal muscle and brain. Splits creatine phosphate in the presence of ADP to produce creatine and ATP. Isoenzymes: MM-fraction (CK-3) present in skeletal muscle and heart muscle, BB-fraction (CK-1) brain, smooth muscle of GIT and urinary tract, MB (CK-2) a maximum of 40% of total CK in heart muscle consists of MB fraction, the rest (60%) being MM isoenzyme. Less than 5% of muscle CK is the MB-isoenzyme.

Interpretation

Marked increases: Cardiac disease: myocardial infarction, myocarditis. Muscular dystrophias.

Moderate increases: Muscle injury: Trauma, surgery, alcoholic myositis, malignant hyperpyrexia, intramuscular injections, hypothyroidism (decreased catabolism), injections. Neurogenic muscle disorders: (i.e. poliomyelitis, myasthenia gravis, etc) are usually not associated with CK increases.

Physiological increases: Neonatal period - During and after delivery.

Aspartate Aminotransferase (AST)

(Previously SGOT - serum glutamate oxaloacetate transaminase)

Reference Ranges: 5-40 IU/L at 37 °C

Physiology

AST and ALT (alanine aminotransferase) are the 2 transaminase enzymes which require pyridoxal phosphate (vitamin B6) as coenzyme. The biochemical function is to transfer amino groups from amino acids to oxo acids. AST is present in decreasing quantities in heart, liver, muscle, pancreas and erythrocytes. Two isoenzymes (cytosolic and mitochondrial) are present in heart and liver tissue.

Interpretation

Marked Increases (> 10 x upper limit of normal)

- Cardiac origin: MI; circulatory failure.
- Hepatic origin: Acute virus/toxic hepatitis.

Moderate Increases

- Muscle injury and disorders: Trauma, surgery, dermatomyositis, general convulsions, severe exercise.

- Hepatic disorders: Cirrhosis, cholestatic jaundice, metastases, infectious mononucleosis.

- Erythrocyte disorders: Severe haemolytic anaemia.

Physiological increases: Neonatal period.

Artefactual increase: In vitro haemolysis.

Alanine Aminotransferase (ALT)

(Previously SGPT - serum glutamate pyruvate transaminase)

Reference Ranges: 5-40 IU/L at 37 °C

Physiology

It is present in high concentrations in liver, and to a much lesser extent in heart and skeletal muscle than AST. In contrast with AST it is only present in the cytosol. The ratio between the two enzymes may be a reflection of the underlying pathology and severity of the disease (see section under "liver enzymes").

Interpretation

Marked Increases

- Circulatory failure, shock by any cause.
- Acute viral or toxic hepatitis.

Moderate Increases

- Liver involvement: Infectious mononucleosis, liver congestion due to CCF, cirrhosis, prolonged cholestatic jaundice.

- Muscle involvement: Extensive trauma or muscle disease. The levels are much less raised than AST.

Lactate Dehydrogenase (LD)

(Previously LDH)

Reference Ranges: 60-200 IU/L at 37 °C

Physiology

Biochemically it catalyses the bidirectional interconversion of lactate and pyruvate. The enzyme is widespread with the highest concentrations being found in the heart, skeletal muscle, liver, kidney, erythrocytes. There are 5 isoenzymes. LD 1 (anodal isoenzyme) predominates in the heart muscle and kidney, LD 5 is the slowest moving (cathodal) isoenzyme and the most abundant form in the liver and skeletal muscle.

Interpretation

Elevated Levels

Marked Increases

- Myocardial infarction, shock.
- Muscular dystrophies.

Moderate Increases

- Malignancies.
- Skeletal muscle disease.
- Pulmonary embolism.
- Hepatitis (infectious mononucleosis).

Artefactual

- Prolonged contact of erythrocytes with plasma or in vitro haemolysis.

Alkaline Phosphatase (ALP)

Reference Ranges: 26-78 IU/L at 37 °C

Physiology

Its biochemical function is to hydrolyze phosphates at a high pH. They are present in osteoblasts in bone, liver, intestine, kidney and placenta. Circulating ALP in adults are mainly derived from liver ($\pm 50\%$) and bone ($\pm 50\%$). In children, especially during the phase of accelerated bone growth, the upper limit of normal can be 5-6 times the adult upper limit. During pregnancy the contribution from the placenta also raises circulating ALP to levels 3 times the upper limit of normal.

Interpretation

Elevated Levels

- Physiological: Children and young adults 2.5 to 6 times the upper limit of normal; pregnancy, last trimester - 2.5 times the upper limit of normal.

- Liver disease: intrahepatic or extrahepatic cholestasis, space-occupying lesions - parasitic granulomas, tumours.

- Bone disease: Paget's disease of bone (may be very high). Osteomalacia and rickets, primary bone tumours and metastases, primary hyperparathyroidism.

Decreased Levels

- Stunted growth: Achondroplasia cretinism, vitamin C deficiency.

- Hypophosphatasia: Autosomal recessive disorder with low ALP and rickets or osetomalacia.

Amylase

**Reference Ranges: Serum 34-126 IU/L at 37 °C
Urine 54-930 IU/L at 37 °C**

Physiology

Its biochemical function is to hydrolyze glycogen to lower molecular weight carbohydrates. It is a low molecular weight stable enzyme (50000 mol mass) and present in high concentrations in the pancreas and parotid glands. In some patients the amylase may be complexed with larger molecules (IgA) which prevents the normal filtration through the glomeruli. In this condition, macroamylasaemia, serum concentrations may be up to 8 times the normal upper limit, and are of no pathological significance.

Interpretation

Elevated Levels

Marked Increase (5-10 x upper limit of normal)

- Acute pancreatitis.
- Perforated peptic ulcer, especially if situated posteriorly.
- Diabetic ketoacidosis.
- Severe renal failure.

Moderate Increase (< 5 x upper limit of normal)

- Acute abdominal conditions: Abdominal trauma, ruptured ectopic pregnancy, torsion of ovarian cysts, acute cholecystitis.
- Salivary gland disorders: Parotitis, calculi.
- Drugs: Morphine (spasm of sphincter of Oddi).
- Renal failure.

Decreased Levels

- Neonates - if elevated it may be due to pathological conditions.
- Chronic pancreatitis.

Lipase

Reference Ranges: 0-190 IU at 25 °C

Physiology

Biochemical function is to hydrolyze triacylglycerols in the presence of colipase. Produced by the exocrine pancreas and to a lesser extent by the GIT mucosa. It is not excreted in the urine due to its molecular mass. The specificity for pancreas pathology is higher than that of amylase. Its concentrations are higher and persists for longer periods than does the elevated concentrations of amylase.

Interpretation

Elevated Levels

Acute pancreatitis or any other abdominal condition with pancreatic involvement, i.e. hepatobiliary pathology, spasm of the sphincter of Oddi, perforation of an ulcer.

Acid Phosphatase (ACP)

Reference Ranges: Total - 0-1 IU/L at 37 °C
Prostatic - 0-4 IU/L at 37 °C

Physiology

In contrast to alkaline phosphatase its hydrolytic activity is optimal at a pH 4.9. ACP is present in the prostate, liver, erythrocytes, platelets and bone. Approximately 1/3 to 1/2 of the total ACP activity in normal men is derived from the prostate. Heparin inhibits the activity of the enzyme and clotted blood should be used for determinations. The enzyme is very unstable and should be analyzed within 3 hours after collection. A variety of isoenzymes have been found in the abovementioned tissues. The prostatic isoenzyme is inhibited by a substrate L-tartarate. The difference between total ACP and tartarate labile ACP represents the prostatic fraction.

Interpretation

Elevated Levels

Artefactual Increase

- Rectal examination: Acute urinary, retention and passage of urinary catheter may increase tartarate labile ACP.
- Haemolysis will increase total ACP.

Pathological Causes

- Disseminated prostatic Ca (tartarate labile ACP).
- Paget's disease of bone (total ACP).
- Thrombocytaemias (total ACP).
- Gaucher's disease (total ACP).

Because of false positives and negatives its clinical usefulness lies in the monitoring of proven cases.

Glutamyltransferase (GGT)

Reference Ranges: 9-34 IU/L at 37 °C

Physiology

It catalyzes the transfer of the glutamyl group between peptides and aminoacids. The highest concentrations are found in the liver, kidney, pancreas, prostate and lung. It is an extremely sensitive indicator of liver disease but can be induced by various drugs, especially antiepileptic drugs and alcohol.

Interpretation

Elevated Levels

- Obstructive liver diseases: Intra- and extrahepatic.
- Hepatocellular disorders, hepatitis, cirrhosis.
- Chronic alcoholism: Induction and liver/pancreas pathology.
- Miscellaneous: MI, pulmonary embolism, diabetes, pneumonia.

Comments

- In contrast with ALP, GGT is not affected in bone disease unless drugs have been used which could induce both GGT as well as an increased metabolic turnover of vitamin D by the liver.

- GGT remains normal during pregnancy.

Plasma Enzyme Patterns During MI

The choice of the most appropriate "cardiac" enzyme depends on the time interval since the onset of the suspected infarction.

A second rise after return to baseline indicates an extension; and a continuation of elevated AST and LD, and a return of CK to baseline reflects liver congestion secondary to CCF.

Table 1.6.2

| Enzyme | Starts to rise (hours) | Time of peak elevation (hours) | Duration of rise (days) |
|--------|------------------------|--------------------------------|-------------------------|
| CK | 3-6 | 24 | 3 |
| AST | 6-12 | 48 | 6 |
| LD | 12-24 | 72 | 10 |

Plasma Enzyme Changes in Liver Disease

The 2 groups of most commonly requested enzymes are **transaminase**, which indicate liver cell damage, and **alkaline phosphatase**, which indicates cholestasis. A plasma ALT activity > AST activity which includes viral hepatitis, alcoholic hepatitis, chronic persistent hepatitis or early chronic active hepatitis. A plasma AST activity > ALT activity includes cirrhosis, advanced chronic active hepatitis. An elevated alkaline phosphatase suggests cholestasis, GGT may be elevated both in hepatocellular damage and cholestasis, however, the transaminase enzymes are more sensitive than GGT.

Plasma Enzyme Abnormalities in Muscle Disorders

Enzymes involved: CK, aldolase, transaminases especially, AST and LD, CK and aldolases are more specific. Elevation of the muscle enzymes are related to:

- The stage of the disease - higher levels earlier in the disease.
- The muscle mass - progressive wasting reduces enzyme levels.
- The age of the patient - muscle enzymes are higher in new-born.
- Muscular activity - during rest enzymes accumulate which are released following muscular activity accentuating the enzyme abnormality.

Enzymes in Malignancy

- LD is widely distributed and therefore may be nonspecifically associated with any malignancy.
- ALP may rise as a result of primary or secondary tumours in liver, bone or may be a tumour product, i.e. Regan isoenzyme.
- Prostatic acid phosphatase is raised in extensive prostatic carcinoma, particularly if metastasized. False positives and negatives detract from its use for diagnosis, however, monitoring diagnosed cases is useful.
- Tumours occasionally produce a number of hormones which can then serve as tumour markers. Among the enzymes most commonly described are CK and ALP.

Table 1.6.3: Tumor Markers

| Marker | Important Malignancies | Nonmalignant disorders |
|------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------|
| I. Oncofetoantigens | | |
| (a) Alfafetoprotein (AFP) | Hepatomas, teratocarcinomas, GIT neoplasms | Pregnancy, liver cell regeneration |
| (b) Carcinoembryonic antigen (CEA) | GIT malignancies, bronchus, GUT and medullary thyroid carcinoma | Smokers, cirrhosis, alcoholism, colitis |
| II. Enzymes | | |
| placental ALP | Ovarium, testes, bronchus | Pregnancy haemolysis |
| LD ACP | Several malignancies Prostate | MI, hepatitis, etc. Rectal examination, hypertrophy prostate |
| III. Hormones | | |
| HCG | Trophoblast tumours, testis and ovarium | Pregnancies, mola hydatidosa |
| Gastrin | Gastrinoma (ZS) | Pernicious anaemia, gastritis |
| IV. Miscellaneous | | |
| Monoclonal gammopathy Waldenstrom | Myeloma, gammopathy macroglobulinaemia | Benign monoclonal |
| Beta2-microglobulin | B-lymphocytes | Glomerulonephritis |
| Ca-125 | Ovarian carcinoma | |

Endocrinology

Thyroid

Free Thyroxine, Free Triiodothyronine, Thyroid-Stimulating Hormone

Reference Range: 0.01-0.03 nanomol/L (10-30 picomol/L)

Physiology

The thyroid gland mainly secretes thyroxine (T₄) and some triiodothyronine. Most of the circulating T₃ is derived from the peripheral conversion (mainly the liver) of T₄ to T₃. The free fractions of the hormones have an inhibitory effect on thyroid-stimulating hormone (TSH) and also reflect the metabolic activity of the thyroid gland. Newer developments in analytical methodology allow the direct determination of the free hormones (FT₄ and FT₃).

Ultrasensitive TSH determinations are now widely available. These assays have a definite lower limit of the reference range in contrast with previous assays. Elevated TSH is the most sensitive test for hypothyroidism and in hyperthyroidism it is associated with a depressed TSH. Thyroliberin provocative tests have been largely replaced by the new TSH assays. The advantage of the determination of the direct free T₄ or T₃ is that interaction with the carrier proteins (pregnancy, drugs, anticoagulants, etc) are largely eliminated.

Interpretation

Table 1.6.4

| Free T ₄ | Free T ₃ | TSH | Diagnosis |
|---------------------|---------------------|-----|-------------------------------------------------------------------------------------------------------------------------------------|
| ↑ | ↑ | ↓ | Primary hyperthyroidism, T ₄ overdose |
| ↑ | ↑ | ↑ | Secondary hyperthyroidism |
| N | ↑ | ↓ | T ₃ thyrotoxicosis, early hyperthyroidism, overdose T ₄ |
| ↓ | ↓ | ↑ | Primary hypothyroidism |
| ↓ | ↓ | ↓ | Secondary hypothyroidism |
| N/↓ | ↓ | N | Euthyroid sick syndromes or early secondary hypothyroidism |
| N | ↓ | N | Diminished peripheral conversion to T ₃ : Propranolol, propylthiouracil, dexamethazone, acute and chronic diseases |
| ↓ | N | ↑ | Early primary hypothyroidism |
| ↓ | ↑ | ↓ | Overdose by T ₃ with hypothyroidism |

Hypertension

Pathophysiology

Hypertensive disorders are characterized by systolic and diastolic blood pressure exceeding 140/90 mm Hg. Although hypertension can be caused by a number of conditions, more than 90% of patients have "primary", "idiopathic", or "essential" hypertension, in which the etiology is unknown. Since hypertension is one of the major risk factors for coronary heart disease and because of the potentiation of atherogenicity when more than one risk factor is present, it is necessary to screen for other risk factors as well, which could also be amenable to therapy. Renal function impairment may also be one of the important consequences of longstanding hypertension and renal function tests are therefore also indicated. Secondary hypertension is identified with a specific disease state responsible for the elevated blood pressure. Only 5-10% of adults with hypertension are secondary. The majority of these subjects will have renal disease and only a very small number of secondary hypertension cases will have pheochromocytoma or primary hyperaldosteronism.

Most of the patients with pheochromocytoma secrete large quantities of noradrenalin which increases peripheral vascular resistance with an elevation of blood pressure. In patients with 11 hydroxylase enzyme deficiency of the adrenal cortex 11 deoxycortisol and 11 deoxycorticosterone accumulate with a resultant mineralocorticoid effect. In Conn's syndrome there is an overactivity of aldosterone, the major mineralocorticoid hormone. Since there is an overlap of function between the glucocorticoids and mineralocorticoids, Cushing's syndrome will also produce hypertension. Hyperthyroidism only causes systolic hypertension and approximately 20-60% of primary hyperthyroid patients have hypertension. The determination of the renin levels are important from the etiological, therapeutic and prognostic point of view. Renin (EDTA-plasma) should be determined with the Na-excretion over a 24 hour period in a patient either in the recumbent or erect position. An elevation of renin levels occurs with malignant hypertension, parenchymal damage, renovascular hypertension, secondary hyperaldosteronism, renin-secreting tumours, oral contraceptive induced hypertension. Decreased renin levels are observed in primary hyperaldosteronism, diabetic nephropathy, heavy metal poisoning, and in approximately 30% of patients with essential hypertension.

Interpretation

Table 1.6.5: Investigation into Metabolic Causes

| | | |
|------------------------------------------------------------------|------------------------------------------------------------------------------------|--------|
| Cause | | |
| Primary (unknown aetiology) calcium and glucose metabolism | Follow up of other risk factor for CHD: (cholesterol, uric acid, renal function | tests, |
| Secondary | | |
| Renal disease examination of the urine for protein casts | ↑ Plasma urea and creatinine, | blood |
| Renovascular | ↑ Plasma renin activity/aldosterone | |
| Endocrine | | |
| Adrenal cortex | | |
| - Cushing's syndrome | ↑ Cortisol | |
| - Congenital adrenal hyperplasia (11 OH-lase deficiency) | ↑ 17 OH progesterone | |
| - Conn's syndrome | ↓ Plasma K ⁺ and ↑ bicarbonate (total CO ₂) | |
| Adrenal medulla | | |
| - Pheochromocytoma metanephrines | ↑ Urinary HMMA (VMA) or 24 hour urinary | |
| Renin secreting tumours | ↑ Plasma renin activity/aldosterone | |
| Severe hyperthyroidism | ↑ Free T ₄ | |
| Primary hyperparathyroidism | ↑ Plasma Ca, ↓ phosphate, Albumin, PTH | |

Gastrin

Reference Range: 0-100 nanog/L

Physiology

Gastrin hormones are produced by the G-cells in the pyloric antrum and the (delta) cells in the pancreas. These hormones are potent stimulants of HCl secretion and are inhibited by a high HCl concentration in the stomach. There are 3 possible indications for gastric determinations:

- Diagnosis of Zollinger Ellison Syndrome (ZES).
- Evaluation of pernicious anaemia.
- Evaluation of pituitary or parathyroid adenomas (multiple endocrine adenopathy type I).

Interpretation

Table 1.6.6.

| Diagnosis | Fasting gastrin | After a meal |
|--------------------|------------------------------|------------------------------|
| ZES | Increase | No further increase |
| G-cell hyperplasia | Increase | Substantial further increase |
| Atrophic gastritis | Increase | Substantial further increase |
| Peptic ulcer | Normal/ slightly elevated | Gradual increase |
| Normal | Normal | Gradual increase |