Current Practice

GROWING POINTS

Radioactive Isotopes in Clinical Medicine—II*

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Studies of Absorption and Distribution

Iron Absorption

Ferrous iron is absorbed from the duodenum and upper part of the small intestine in quantities that depend on the body needs. Thus as the iron stores fall more iron is absorbed. Ferric iron must be reduced to the ferrous state before it can be absorbed, and ascorbic acid, among other reducing agents, will achieve this. Iron is not absorbed by diffusion but by a specific carrier protein within the intestinal cell called apoferritin, which binds the ferrous iron into a protein complex, "ferritin," in which the iron is in ferric form. This apoferritin-ferritin cycle regulates iron absorption and prevents iron overloading, for, once absorbed, iron cannot be excreted in appreciable amounts. After absorption iron becomes attached to a beta-globulin called transferrin, and is cleared quickly from the plasma by the bone marrow, where it is incorporated into the haemoglobin molecule of the developing erythrocyte. The total serum-iron level remains at about 120 µg. per 100 ml., and transferrin is normally only one-third saturated. Iron excreted in the faeces represents the amount unabsorbed, and a measure of the fraction absorbed may therefore be obtained from the difference between the amount in the faeces and the dose given by mouth. Normally the amount of iron absorbed is not more than 30%, but in iron deficiency this figure may increase to 80%. Seventy to one hundred per cent. of the absorbed iron will reappear in the circulating erythrocytes within a period of ten days. The remainder is deposited as iron stores in the form of ferritin or haemosiderin in the liver, spleen, bone marrow, and reticulo-endothelial system.

Studies of the absorption of radioactive inorganic iron salts in a fasting subject give information of only limited value, for ferrous salts are absorbed more readily than food iron in both normal people and patients with iron deficiency. Indeed, in patients who have undergone partial gastrectomy food iron may be absorbed poorly but ferrous chloride readily. The difference is due in part to the necessity of reducing the food iron to the ferrous form before absorption takes place, and in part to the solid content of the test meal and the formation of insoluble iron compounds, such as phytates and phosphates, when the iron is taken in food. In order to study iron absorption under natural conditions, the absorption of iron incorporated biosynthetically into foods, such as eggs and vegetables, may be studied, but the labelling process is tedious. Tests of iron absorption have therefore been developed in which the labelled iron is added to a meal of standard iron content. Though this is not an exact reproduction of the conditions by which food iron is absorbed, it has been shown to provide a reliable measure of absorption of dietary iron.

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Double Isotope Technique

A double isotope technique for measuring iron absorption has recently been introduced, and this obviates the necessity of stool collection. One isotope of iron (Fe-59) is injected intravenously, and another isotope (Fe-55) is given by mouth at the same time. The intravenous isotope is used to determine the percentage of plasma iron that is used for haemoglobin synthesis: this is the amount which appears within the circulating red cells after a period of ten days. From the relative amount of the orally administered isotope in the red cells at the same time it is possible to calculate the amount of oral isotope that has been absorbed. Both the isotopes of iron can be counted separately. Liquid scintillation counting is required for the iron-55, and this necessitates separating the iron from the blood by a process of digestion and precipitation. The accuracy of these methods is reduced if iron is not absorbed adequately, or, if as a result of iron overloading, the radioactive iron does not appear in the circulating haemoglobin in an appreciable concentration.

A happy solution to many of the problems of absorption in haematological studies, and indeed in the studies of absorption in general, is the development of a reliable whole body counter. The measurement of total body radioactivity immediately after a dose of a radioactive isotope, and then again a week or more later, provides the information necessary to determine the amount absorbed. A suitable body counter would obviate the need for stool collections, and, as it would mean counting body radioactivity on only two occasions, it would be ideal for out-patient use. It is obviously important that the count recorded should always be proportional to the radioactivity in the body and independent of any localization of this radioactivity. The crystal must therefore be placed at a distance from the patient. The use of two detectors, one above and one below the patient, has improved the accuracy of such a total body counter. Rapid developments are taking place in the field of counting whole body radioactivity, and there is little doubt that this method will provide the most acceptable and accurate measure of absorption of radioactive compounds before long.

Vitamin-B₁₂ Absorption

Certain species of streptomyces synthesize vitamin B₁₂, a vitamin containing one atom of cobalt per molecule. If radioactive cobalt is added to the culture medium of the organism the synthesized vitamin is radioactive. Pernicious anaemia is characterized by a deficiency of intrinsic factor, and vitamin B₁₂ cannot be absorbed from the ileum unless intrinsic factor is present. The radioactive cobalt bound to the vitamin may be traced after its oral administration, and if the labelled vitamin is absorbed then intrinsic factor must be present. The reverse, however, is not necessarily true, because vitamin B₁₂ may not be absorbed on account of intestinal disease, such as regional ileitis,

malabsorption syndrome, or tropical sprue. The principle of the test is to give labelled vitamin B₁₂ by mouth and to calculate the amount absorbed. This may be done by counting the amount excreted in the faeces, a normal person losing 20–50% of the administered dose, while a patient with pernicious anaemia loses 85–100% of the dose. An alternative method is to measure the concentration in the blood after the administration of an oral dose, though this requires a larger dose of isotope. The favoured test is, however, the Schilling test, which measures the urinary excretion of isotope. This test depends on detecting in the urine the amount of isotope that has been absorbed into the blood and excreted by the kidney. To prevent accumulation and storage of the radioactive vitamin in the body a large dose of non-radioactive vitamin B₁₂ (1,000 µg.) is given parenterally about an hour or two after the oral administration of the labelled vitamin. Urine is collected for 48 hours and the radioactivity measured. A normal person will excrete 15–50% of the administered dose, but a patient with pernicious anaemia less than 7%. The Schilling test is not reliable if there is renal failure. Repetition of the test after the administration of intrinsic factor will restore absorption to normal in the patient with pernicious anaemia, but will not improve the malabsorption of vitamin B₁₂ secondary to states of intestinal malabsorption. An alternative method of measuring vitamin-B₁₂ absorption is to determine the liver uptake by external counting after an oral dose of labelled vitamin B₁₂.

The cobalt isotope originally used was cobalt-60, which has a half-life of five years. Other isotopes of cobalt have a shorter half-life and permit larger doses to be given and hence enable plasma levels to be determined. Cobalt-58 with a half-life of 71 days has been used for this purpose. Peak plasma concentrations occur 8 to 12 hours after an oral dose in a normal person.

Intestinal Fat Absorption

Fats labelled with iodine-131 have been used to determine the digestive and absorptive capacities of the intestinal tract. By giving triolein labelled with iodine-131 by mouth it is theoretically possible to estimate the unabsorbed fraction of fat in the faeces over a period of 48 hours. There is, however, little correlation between the degree of malabsorption as estimated by labelled triolein and that obtained by the chemical determination of fat excretion in patients with steatorrhoea. This is hardly surprising, as dietary fat consists of a mixture of long- and short-chain saturated and unsaturated fats and triolein may not be representative of these. Furthermore, the iodine label may become detached from the triolein and absorbed separately. Hence some patients with steatorrhoea appear to "absorb" labelled triolein normally. Thus the clinical application of the isotope method is limited, and the chemical estimation of fat excretion remains the most reliable test of steatorrhoea. Nevertheless, it is true that most patients whose excretion of labelled triolein exceeds 5% of the administered dose have malabsorption. Carbon-14-labelled fats have been used in research studies on animals; the half-life of the isotope is, however, over 5,000 years, so that the hazard of radiation precludes its general use in man.

Isotopes in Dilution Studies

The body content and distribution of water and electrolytes may be measured with the appropriate isotope, using the dilution principle. The estimation of plasma volume, red-cell volume, and exchangeable body sodium and potassium is largely restricted to research purposes. Nevertheless, the measurement of the plasma volume may be of value in states of dehydration following burns, in chronic protein deficiency, and in congestive cardiac failure. In states of dehydration the serum electrolyte concentrations are no reflection of the body content

of the electrolytes. In polycythaemia rubra vera the red-cell volume is always increased and may often be twice normal. Occasionally there is a concomitant increase in plasma volume, so that the concentration of the haemoglobin and the packed cell volume may be near normal, though the total red-cell mass is greatly increased. In these situations the estimation of the red-cell volume may be of great value. A known quantity of red cells labelled with chromium-51 is injected, and a sample is taken 10 minutes later, when mixing has occurred. The red-cell mass may then be estimated from the degree of dilution that has occurred. The increased red-cell mass is an important diagnostic criterion to differentiate polycythaemia rubra vera from most of the secondary polycythaemias, in which the haemoglobin is raised but the red-cell mass is normal.

Similarly the concentration of electrolytes in the blood is not a true guide to the body's content of these elements if the plasma volume is altered. Plasma-volume determinations may then be helpful. This is done by injecting a known quantity of iodine-131-labelled human serum albumin into the circulation and withdrawing blood at a suitable interval after injection to measure its dilution and so estimate the plasma volume. Since human serum albumin will ultimately diffuse into the extracellular space, the specimens of blood for estimation of the isotope dilution must be withdrawn as soon as possible after mixing in the blood, and this is usually done at about ten minutes. If longer intervals are allowed to elapse there may be diffusion of the albumin into the extracellular space.

Isotope studies are useful for the measurement of exchangeable body potassium. As 90% of the body potassium is intracellular, the serum concentration is a poor indicator of the total body potassium, especially if an associated loss of sodium has led to reduction of the extracellular volume. The isotope potassium-42 equilibrates with intracellular exchangeable potassium in about 24 to 48 hours. From the dilution of the isotope injected, therefore, the total exchangeable body potassium can be calculated.

Physical Tracing Studies

Red Cell Survival

Chromium, as sodium chromate, readily penetrates red blood cells and becomes firmly bound to the globin portion of the haemoglobin molecule. Labelling of red blood cells with chromium-51 permits evaluation of red-cell survival, and this method has replaced the Ashby differential agglutination technique, which could not be used to study the survival of a patient's own cells in his own circulation. The procedure involves withdrawal of a 20-ml. sample of blood and adding the isotope. An interval of 30 to 60 minutes allows the chromium to become attached to the haemoglobin of the red cells. The cells are then washed with normal saline, and a known amount of the labelled blood is reinjected. Samples are taken at intervals on subsequent days over the next two weeks. When the logarithm of the radioactivity (counts per minute) is plotted against time the points lie on a straight line and the time taken for half the radioactivity to disappear is apparent. The results of cell survival are usually expressed in terms of the half-time disappearance of the chromium isotope; the normal is about 28 days. Though this apparent survival curve differs appreciably from the survival curve obtained by the differential agglutination method, the results with chromium-51 are consistent and more accurate. The difference is largely due to the fact that chromium elutes from the red cells at a constant rate. Because this rate is constant it can be allowed for. Formulae are available for calculating the mean cell survival from these data. These calculations are accurate if cell survival is short but are less reliable when the cell life approaches normal.

In patients with a haemolytic process the site of red-cell destruction can be recognized by in-vivo surface counting, and this is an invaluable procedure before submitting a patient with

FIG. 4.—Brain scan in which the mechanical printing of coloured marks is determined by the radioactive count rate. The highest counting rates are recorded by blue marks and lesser rates by purple, red, yellow, green, and finally black marks. The brain tumour is visually portrayed by the high count rates. The high count rates below the dotted line are due to the radioactivity in the facial muscles.

haemolytic anaemia to splenectomy. Moreover, by measuring the survival of normal group O cells in the patient's circulation and the survival of the patient's cells in a normal compatible recipient, the nature of the haemolytic disease can be assessed. If, on the one hand, the patient's cells survive normally in a recipient then the haemolysis must be due to a lytic factor in the patient's serum. If, on the other hand, the patient's cells do not survive normally in the recipient the cells must be abnormal. The red cells from normal donors will survive their usual span in patients with diseases such as congenital spherocytosis, sickle-cell disease, or paroxysmal nocturnal haemoglobinuria, where the haemolysis is due to intrinsic defects in the red cells. Conversely, spherocytic or sickle cells will be rapidly destroyed when transfused into normal people.

Leucocytes may also be labelled with chromium-51 and their survival measured. Various isotopes have been used for the measurement of platelet survival, but the in-vitro labelling of isologous platelets with chromium-51 has been the most extensively employed. A normal platelet survival of 8–10 days is obtained, and in idiopathic thrombocytopenic purpura the survival is found to be constantly reduced, being 1–3 days in the chronic varieties and shorter in more acute forms. The number of platelets in the peripheral blood has been shown to depend exclusively on the rate of platelet destruction. A compensatory increase in bone-marrow production does not seem to occur, as it does with the red-cell series in haemolytic disease. This suggests that the autoantibodies which influence the destruction of platelets also affect megakaryocyte function.

The labelling of red cells with chromium-51 also provides a sensitive measure of gastrointestinal bleeding, as normally only negligible amounts of radioactivity can be detected in the faeces in patients whose cells have been labelled with radioactive chromium. A comparison of the amount of chromium-51 in the stool with that in the circulating blood yields a quantitative figure of the volume of blood being lost.

Left to Right Cardiac Shunts

The radioactive gas krypton-85 may be used to detect intra-cardiac shunts. The gas is administered to the patient by inhalation and is carried through the pulmonary capillaries and veins to the left atrium. The instant at which the gas is inhaled is recorded by a Geiger counter placed in the inflow to the face mask. Blood from the right side of the heart is withdrawn through a cardiac catheter and directed through a scintillation counter, so that the moment of the appearance of radioactivity in the right side of the heart is also recorded. If there is no shunt the time interval is equal to the complete circulation time—that is, 15–25 seconds—whereas if there is a left to right shunt present the time interval is shorter—namely, about 5 seconds.

Determination of Blood Flow

The clearance of a freely diffusible indicator from extracellular tissue is determined only by the blood supply, and hence is a measure of local blood flow. This principle has been used to measure the blood flow in skeletal muscle, employing the radioactive gas xenon-133. The xenon is dissolved in saline and injected directly into muscle tissue; subsequently its clearance rate is measured by placing a scintillation counter directly over the injection site. This technique permits a clear-cut differentiation between legs with a normal circulation and limbs with occlusive vascular disease.

Lung-function Studies

It is sometimes desirable to measure the function of small regions of lung as, for example, in assessing the pulmonary

disability being caused by localized bullae. This may be done using the radioactive gas xenon-133. The radioactive xenon is dissolved in saline and injected through a catheter either into the femoral vein or the superior vena cava. When the xenon reaches the pulmonary capillaries it becomes transferred into alveolar gas because of its low solubility. The radioactivity is detected by scintillation counters placed at different areas over the chest, and the regional perfusion may be evaluated from the maximum counting rate. The regional ventilation may also be assessed from the rate of disappearance of the radioactivity from the region.

Scanning of Organs and Tissues

Brain Tumour Localization

Attempts have been made recently to discover compounds which will localize in tumour tissue. By labelling these compounds with a radioactive element it would then be possible to identify and locate such tumours. Useful preparations are now available for the detection of brain and liver tumours. For brain tumours chlormerodrin labelled with mercury-197 has been used with good effect. The localized concentration of this substance in tumours probably results from a breakdown of the vital barriers that prevent the entrance of certain substances into normal tissue.

Iodine-131-labelled human serum albumin has also been used to detect brain neoplasms, but in this instance the selective concentration in the tumour is not due to a breakdown of normal cell barriers but reflects the greater proportion of extracellular fluid, which is characteristic of tumour tissue in the brain. Radioactive technetium is also distributed in extracellular fluid, and, with its suitable energy and shorter half-life, it promises to be a useful isotope for the detection of brain tumours. Most tumours (80% confirmed positives) can be detected and localized by this method, but, as the radioactive compound must reach the tumour through the blood, vascular and inflammatory masses will also show a high uptake of radioactivity, so that it may be impossible to distinguish them from tumours. A technique such as this, which causes little distress to the patient, is likely to replace air-studies and cerebral angiography as screening procedures. Brain scanners are now available in which the distribution of radioactivity is displayed by the mechanical printing of coloured marks. The colour of the mark at any point is determined by the counting rate detected by the scintillation scanner at that point. Six colours may be selected from a multicoloured ribbon. The highest counting rates are recorded by blue marks and lesser degrees of radioactivity are represented by purple, red, yellow, and green marks, and the lowest rates by black. Quite small variations in the colour pattern are visible to the human eye and the tumour may thus be visually portrayed (Fig. 4, Special Plate).

Other Tumours

Tumour masses may be identified in the liver by using an isotope which is taken up by normal liver cells and which will thus reveal tumours as "cold areas." As the Kupffer cells extract colloid particles from the blood, colloidal gold, labelled with gold-198, is taken up by the Kupffer cells and fixed there, so that a subsequent scan will show a reduced uptake if there is a tumour, abscess, or cyst. Rose-bengal is a dye rapidly taken up by liver cells and excreted into the bile. Tumours and masses, which do not contain functioning liver tissue, will not take up the dye. When the dye is labelled with iodine-131 tumours appear as "cold areas" on the radioactive scan. Hepatic scans may provide information about the size, shape, position, and internal detail of the liver. Their major application is in the diagnosis of localized disease or space-occupying

lesions within the liver. Nevertheless, equivocal results from such scans are unfortunately frequent.

Chlormerodrin labelled with mercury-197, being concentrated in the renal tubules, has been used for the detection of renal tumours. These, being "non-functioning" renal tissue, will appear as "cold areas" on the radioactive scan. Renal abscesses and cysts cannot, however, be differentiated from tumours on a radioactive scan. Furthermore, renal scanning does not give the anatomical detail of arteriography, and hence its application is limited.

Selenomethionine labelled with selenium-75 behaves like the amino-acid methionine, and can be made to localize in pancreatic tissue. The normal pancreas takes up the isotope uniformly, but tumours may appear as "cold areas" on the radioactive scan, and in chronic pancreatitis there is often diffuse inhibition of isotope uptake. Unfortunately the liver also takes up the isotope, and it is necessary to precede this investigation with a liver scan, using colloidal gold labelled with gold-198, to determine the position of the liver edge. It is premature to assess the value of this method of detecting pancreatic tumours, but the diagnosis of tumours in this region is notoriously difficult, and, as the pancreas remains one of the few organs defying radiological demonstration, the value of an isotope method would be great.

Other Applications

Red blood cells damaged by heat are rapidly destroyed in the spleen. If such cells are labelled with chromium-51 and re-injected subsequent in-vivo counting over the spleen area will enable the position of the spleen to be delineated.

Pulmonary emboli may be detected by lung scanning after the intravenous injection of macro-aggregated human serum albumin labelled with iodine-131 or radioactive technetium. Ischaemia is produced in those regions of the lungs supplied by the obstructed vessel, and the lung scan is able to demonstrate these ischaemic changes as "cold areas" before they are of sufficient magnitude to be apparent on radiography.

Isotopes in Treatment

Thyrotoxicosis

There is no doubt that iodine-131 therapy is the most convenient form of treatment for the patient with thyrotoxicosis, as it entails merely drinking some tasteless fluid. The chief consideration which limits its use in thyrotoxicosis is the fear of inducing malignant changes in the thyroid gland subsequently. There are, however, no reports of cases of carcinoma which can be attributed to iodine-131 therapy for thyrotoxicosis despite the treatment of many thousands of patients during the last 25 years. Nor does the incidence of leukaemia exceed that which would be expected on the basis of chance association. Nevertheless, the possibility of radiation-induced mutations occurring after 25 years cannot be excluded, and it has been the practice in Britain to limit this form of treatment to patients over the age of 40 years, those with a life expectancy of less than 20 years, or those in whom there is some good reason to avoid surgery. Radioactive iodine therapy should not be used in thyrotoxic children nor in a patient who is lactating or who might be pregnant.

One of the disadvantages of this form of treatment is the increased incidence of myxoedema that develops subsequently. Within the two-year period following treatment the overall incidence of hypothyroidism is 9%, which differs little from that following surgery. With the passage of time, however, it increases steadily, and after eight years the incidence of hypothyroidism is 30% and ultimately it may reach 40–50% of the patients treated.

Radioactive iodine therapy has also been used for euthyroid patients with incapacitating angina of effort or refractory congestive cardiac failure. By inducing hypothyroidism, and thus lowering the rate of metabolism, the demands on the heart are reduced. This may benefit patients with refractory cardiac failure. The advent of propranolol has reduced the application of this form of treatment for patients with angina of effort.

Carcinoma of the Thyroid

The most effective treatment of carcinoma of the thyroid is complete surgical excision. If this is not possible or practicable, iodine-131 therapy may be used for the well-differentiated tumours, and external irradiation if the tumour is undifferentiated. When iodine-131 therapy is used all normal thyroid tissue must first be destroyed with a large dose of iodine-131 (75 to 100 mCi), so that with a subsequent dose the tumour cells will be encouraged to concentrate sufficient iodine-131 to effect their self-destruction.

Radioactive Phosphorus

After administration phosphorus-32 passes to tissues that have a high phosphate content and which metabolize phosphate rapidly. It is therefore largely deposited in bone as calcium phosphate, for this comprises the major phosphate pool in the body, and it is also incorporated into the nucleoproteins of nuclei of rapidly dividing cells. This includes bone-marrow cells, particularly when the mitotic rate is increased as in polycythaemia rubra vera and leukaemia. Irradiation of the bone marrow will result from both these processes, and since phosphorus-32 has a half-life of 14.5 days this will last for several weeks. Phosphorus-32 disintegrates with the emission of a beta particle, and thereupon becomes stable sulphur. This beta particle can penetrate tissue to 7 mm., and this is how phosphorus-32 exerts its radiation effect. As with deep x-ray therapy, it is not possible to give enough phosphorus-32 to destroy all leukaemic cells without also destroying erythroid cells and megakaryocytes. In leukaemia radioactive phosphorus is of value only in the chronic myeloid variety, and even in this condition it is not as effective as busulphan (Myleran). Its greatest therapeutic application is in polycythaemia rubra vera, in which remissions of the disease can be achieved in most cases. Radioactive phosphorus does not begin to have effect for 30–60 days after administration, and thus the packed cell volume should first be reduced by venesection. Remissions of several years after a single dose are common. Four to five millicuries of phosphorus-32 should be given intravenously, and the position reviewed after a month or two, though no further dose should be allowed for a period of three months.

One disadvantage of this form of therapy is that the incidence of leukaemia in patients with polycythaemia rubra vera treated with phosphorus-32 is higher than in patients treated by other means. If polycythaemia rubra vera is untreated patients survive for about five years and death is usually the result of thrombosis or haemorrhage, particularly in the cerebral and coronary vessels. A few patients will develop myelosclerosis or acute myeloblastic leukaemia as a natural outcome of the disease. With phosphorus-32, on the other hand, the mean survival has been increased from 5 to 15 years and it is possible that part of the increased incidence of acute leukaemia in those treated patients is related to the reduction of thrombotic and haemorrhagic causes of death. On the other hand, the incidence of leukaemia after the treatment of polycythaemia rubra vera with busulphan (Myleran) or pyrimethamine (Daraprim) is not increased, though the mean survival of such patients is precisely the same as after radioactive phosphorus. Cytotoxic drugs have their own hazards and phosphorus-32, because of its ease of administration and absence of other serious side-effects, remains preferable except perhaps in

the younger patient. Venesection is the quickest way of reducing the red-cell mass and should always be tried first.

Teletherapy

In cobalt teletherapy the isotope cobalt-60 is used to deliver 1.2–1.3-million-volt radiation, which is equivalent to x rays generated at a peak voltage of 3 to 4 million volts. Cobalt “bombs” have replaced radium units, since cobalt-60 may be prepared by activation of stable cobalt in a nuclear reactor, which is more economical than the use of naturally radioactive radium—which is scarce and expensive and does not have the same intensity of radiation. The only disadvantage of cobalt compared with radium is that its half-life is a good deal shorter. Radium has a half-life of more than 1,500 years, but the half-life of cobalt is 5.3 years, so that the isotope has to be replaced in cobalt units from time to time.

Implant Techniques

Several isotopes can be made up into needles for implantation, and the emission of their gamma rays provides local irradiation; cobalt is a good substitute for radium for this purpose and both are used in the treatment of carcinoma of the uterine cervix. Tantalum is more malleable than cobalt, and is preferable for use in wires to implant tumours of curved surfaces such as the bladder. It can be bent into any shape or form.

Radioactive gold (Au-198), as gold wire, may be cut into short pieces and has replaced radon seeds. The short half-life has an advantage of enabling the implant to be left in place permanently and not removed at a subsequent operation.

Yttrium-90 has been used as an implant for the pituitary to irradiate the gland, particularly in patients with carcinomatosis from primary growths in the breast and prostate. It has the advantage of avoiding operation, as the implant can be passed through a needle into the sella turcica through the nose and the sphenoidal sinus under radiological control. This is not without hazard and hypophysectomy probably carries no greater risk.

Radioactive Solutions Injected into a Cavity

In certain types of bladder tumour where there is diffuse disease and where total cystectomy is not desirable the bladder may be irradiated from within by injecting colloidal gold labelled with gold-198. There is no systemic absorption of the colloidal solution and it may, diluted with urine, be removed after three hours, when adequate irradiation will have been achieved.

Gold-198 has been used as a colloidal solution to prevent the reaccumulation of malignant effusions of the pleura and peritoneum. The indications for intrapleural and intraperitoneal administration of radioactive isotopes have been reduced since the introduction of more recent cytotoxic drugs such as cyclophosphamide.

MEDICINE TODAY

Babies at Risk

“Medicine Today” is the television series for doctors produced by the B.B.C. Advice in the preparation of the programmes is given by the Association for the Study of Medical Education.

The programme on B.B.C. 2 on 23 May was on the examination of the newborn baby. Printed below is an article prepared with the help of expert contributors to complement the television programme, which will be repeated on B.B.C. 1 on 30 May at about 11.30 p.m.

Premature or Dysmature?

In *Medicine Today* Dr. F. S. W. Brimblecombe showed how, thanks to French workers,^{1–4} neurological examination can go a long way to distinguishing the true premature baby from the dysmature baby—the baby who is “small for dates”—born at or near term but with a low birthweight. Certain physical features, such as the consistency of the cartilage of the ear, also help one to distinguish these babies.⁵ There are those, however, who think that all this is just an academic exercise, interesting, but of no practical importance. Their idea is far from the truth. The dysmature baby is a child “at risk” to various hazards.

In the first place, the dysmature infant has a somewhat more tenuous hold on life in the newborn period than the premature baby.^{6,7} He is more liable to hypothermia,⁸ especially if he is (wrongly) starved for the first 48 hours or kept on a low-calorie diet. This may be due to depletion of brown adipose tissue. He is probably more liable to suffer a cerebral haemorrhage. He is more liable to have cyanotic attacks—of which an important cause is hypoglycaemia.

Hypoglycaemia

The risk of hypoglycaemia developing in a dysmature baby is greatest towards the end of the second day.^{9,10} There may or may not be overt symptoms—especially twitchings or fits, cyanotic attacks, or just irritability. The hypoglycaemia may be asymptomatic, but it may nevertheless harm the infant's brain. It is well recognized that severe hypoglycaemia, such as that caused by insulin overdosage, may cause irreversible brain damage. Many now feel that hypoglycaemia in the newborn may well partly explain the higher incidence of mental subnormality in small premature babies, and especially in dysmature babies, than in full-term babies of normal weight. Alison McDonald⁶ found that fits are five times more frequent in dysmature babies than in premature ones, and subsequent mental subnormality was twice as common. In one large study¹¹ three times more dysmature babies had an I.Q. below 90 at school age than did premature babies. It is known,^{12–14} furthermore, that the smaller of twins is particularly apt to suffer hypoglycaemia and that the smaller of twins is usually less intelligent than his larger cotwin. It follows that dysmaturity should be a warning of the possibility of hypoglycaemia and that a routine blood sugar estimation should be carried out on dysmature babies in the second day, and especially in the smaller of twins. Toxaemia of pregnancy is one of the antecedents of dysmaturity and so of hypoglycaemia.¹⁵

Congenital Anomalies

Dysmaturity is associated with^{7,16–18} a higher incidence of congenital anomalies than is true prematurity. These include