# RADIOPAQUE DIAGNOSTIC AGENTS[1,2]

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## General

If pharmacology is defined as the study of the action of drugs, then the study of radiopaque diagnostic agents, or contrast media for radiography, can scarcely be regarded as a part of pharmacology. The perfect radiopaque diagnostic agent will enter and leave the body without altering its functions; however, perfect agents are seldom found. Another reason justifying the inclusion of the study of these agents in pharmacology is that their fate in the body determines their usefulness. This recognized branch of pharmacology (*vide* Schmiedeberg), "the fate of substances in the body", has been viewed by the writer as lachesiology which is well exemplified by these compounds. This term seems suitable as Lachesis was, to the Greeks, that one of the Fates who took the thread of human life and wove it into the fabric of existence. Her name is doubly suitable as she also measured the length of the thread.

The field of radiopaque diagnostic agents is as old as radiography. Soon after Roentgen's report of his discovery of the X ray, attempts at medical application revealed its limitation by the roughly-equal absorption of these rays by the soft parts of the body, that is, those other than bone or air containing regions, so that they were not made visible. About one year after Roentgen's report, descriptions of the use of contrast media had appeared. As for the literature, the most extensive review is that of Hecht (1) which appeared in 1939. The review of Dorn (2) is comprehensive, especially from the chemical standpoint. A monograph by this writer (3), appearing in 1961, dealt particularly with the period 1939 to 1958. A conference on radiopaque diagnostic agents was held by the New York Academy of Sciences in October, 1958, and the papers presented there appeared in 1959 (4). A review appearing in *Medicinal Chemistry* (5) lacks the exhaustive chemical coverage which one expects of that series. A summary of the field in the Czech language appeared in 1964 (6). For the present review, the literature has been examined through mid-1964.

Documentation of these agents is often far from what would be desired. It seems that the development of a new agent often consists of (*a*) preparation of an organic compound with high iodine content, (*b*) demonstration that the acute lethal toxicity of the compound in animals is low, and (*c*) introduction of the compound into clinical trial with the subsequent appearance of numerous papers of the testimonial type, without any comparison of

[1] The survey of literature pertaining to this review was concluded in July, 1964.
[2] The following abbreviations will be used: GFR (glomerular filtration rate); PAH (*p*-aminohippurate); and RPF (renal plasma flow).

the new agent with existing ones. Apparently this procedure has been considered adequate for the introduction of a new compound, but it contributes less to an understanding of the field than one would wish. A valuable description of the evaluation of iodinated organic compounds as radiopaque media has been given by Hoppe (7). In general, the following properties are sought.

*Physical.*—The absorption of X rays should be high. For a molecule, this is a function of the percentage composition and the atomic numbers of the elements, but not of the manner in which they are held in molecular combination. Of the media found to be useful, none owes its radiopacity to an element with atomic number less than 35 (bromine), as absorbing too little, or greater than 56 (barium), as being too toxic. An exception to the generalization that absorption is related to the atomic number is provided by the presence of absorption discontinuities, as is seen with iodine. Attempts have been made to use compounds of bromine rather than those of iodine to take advantage of the greater absorption of bromine at longer wave lengths; but this advantage cannot be realized in practice, because the penetration of the body by these long wave lengths is inadequate (8) so that no compounds of bromine are currently in use.

*Chemical.*—Except for barium sulfate, all opaque media which are now in use are compounds of iodine, since it has a suitable radiopacity and can be incorporated into a variety of organic compounds, the structure of which will determine their fate in the animal body. They should be prepared free of inorganic iodine and should remain so before use and after entrance into the body. The radiopacity of organic iodine compounds is proportional to their iodine content.

*Biological localization.*—If instilled into the alimentary or other tract, the substance should remain in it to the extent, and for the length of time, necessary to permit its visualization. If injected into the body, it should localize specifically such as in the liver or kidney, or their excretory ducts.

*Pharmacodynamics.*—Desirably there should be no pharmacological actions either locally at the point at which it is applied, or generally, at the tissues which it eventually may reach. The substance should be devoid of toxicity in terms of damaging tissues locally or of producing 'side effects' such as nausea, vomiting, diarrhea, syncope, allergic manifestations, or death.

*Elimination.*—Elimination should be prompt, once the purpose has been served.

## Alimentary Tract

*Barium sulfate.*—Barium sulfate has maintained its popularity as it is effective, nontoxic, and cheap. Although other barium salts are highly poisonous, little sign of toxic action of the sulfate appears in feeding experiments in animals (9, 10). A review in 1923 (11) of 130,000 cases reported no harm. Since then, many tons of the substance must have been ingested. This low toxicity is no doubt referable to its insolubility and lack of absorption. The latter is, however, not zero (12), as 0.3 to 0.7 mg per kg was found in rats

receiving $BaSO_4$, 1 to 2.25 g administered over 2 to 5 days and killed 1 to 2 days later. These values probably underestimate those amounts absorbed, since rapid excretion follows parenteral administration, about 30 percent being excreted by the alimentary tract in the first 24 hours. Perhaps the chief fear is the occurrence of accidents, particularly perforation. Frimann-Dahl (13) reports five cases of intestinal perforation who were given $BaSO_4$ without fatal outcome and concludes that $BaSO_4$ may be administered in cases of obstruction. However, other reviewers (14, 15) describe cases of perforation in which subsequent formation of adhesions and obstruction required repeated surgery. Sudden death (16) and minor difficulties may follow a $BaSO_4$ enema, but these seem to be largely attributable to the misuse of that dangerous instrument, the enema nozzle.

Earliest observations with $BaSO_4$ were of the outline, motility, and defects of stomach and intestine. Technical improvement in apparatus has permitted demonstration of the mucosal pattern by distribution of a small amount of medium over the mucous membrane. Experience showed great variation in success of this procedure, and attention has been directed to constitutional factors in the subject, the form of the barium sulfate and adjuvants to it. An important contribution to this subject was that of Frazer, French & Thompson (17) who showed that mucous secretions of the alimentary tract would produce agglomeration of $BaSO_4$ *in vitro*. Subsequent papers (18, 19) showed that flocculation of $BaSO_4$ was characteristic of idiopathic steatorrhea and other alimentary disorders. It was claimed that a particular preparation of $BaSO_4$ ("Raybar", which was not described further) did not flocculate *in vitro* with freshly secreted mucus and also did not flocculate *in vivo*. It was also reported that the addition of carboxymethylcellulose produced a nonflocculating suspension which could be used to demonstrate mucosal pattern. Subsequent investigation (20, 21) confirmed many of these findings. Human gastric contents may have an intense agglomerating effect on barium sulfate, apparently through adsorption of mucoprotein by the $BaSO_4$. That this agglomeration occurs *in situ* to impair mucosal visualization is indicated by the observation of an inverse correlation of excellence of mucosal visualization with volume of gastric contents. However, this correlation was less than perfect, indicating that other factors operate to determine the success of this procedure. Numerous preparations of $BaSO_4$ with varying particle size are commercially available and claims for superiority have been made. These are, in general, without factual support derived from comparative studies.

Controlled comparative studies (22) revealed that no advantage accrued from the use of barium sulfate of a particle size less than $BaSO_4$ USP, although larger particles gave poorer results. Studies of adjuvants (20) gave additional evidence that agglomeration interferes with mucosal visualization. For example, Tween 80 was not effective *in vitro* in preventing agglomeration and *in vivo* gave poorer results than $BaSO_4$ alone. Methylcellulose was inferior both *in vitro* and *in vivo* to cellulose derivatives with ionic groups

(carboxymethylcellulose and cellulose sulfate). Lecithins reduced agglomeration and improved visualization. Magnesium aluminum silicate (Veegum) reduced agglomeration but gave poor visualization; the high viscosity of this material may have been important.

One possible disadvantage of $BaSO_4$ is that its highly viscous suspensions may not penetrate small lesions. It may be of advantage here to prepare $BaSO_4$ which gives a suspension of low viscosity. The viscosity of a suspension of $BaSO_4$ is said to be proportional to the effective concentration, where this refers to the total volume of solid together with the water trapped within clumps of particles (23).

*Iodine Compounds.*—An additional attempt to overcome this disadvantage of $BaSO_4$ and to provide other advantages has been the introduction of organic iodine compounds for use in the alimentary tract (4, 24). These compounds, particularly diatrizoate sodium, are true solutions in water; they are miscible with intestinal contents and with blood, do not leave a dry residuum such as may lead to impaction as does $BaSO_4$, and, if they enter the peritoneal cavity, they will be absorbed and excreted without harm. Their lower viscosity may permit penetration of small lesions more readily than with a $BaSO_4$ suspension. These substances are very little absorbed from the alimentary tract (24, 25, 26), undoubtedly because they are relatively-strong acids with low lipoid solubility (27). This conclusion is supported by the observation that addition of alkali reduces absorption. These materials are osmotically active (which $BaSO_4$ is not); thus, they are rapidly diluted in concentration in the small intestine so that it is not well visualized. This introduction of an osmotically-active unabsorbed material often leads to diarrhea. Unless material advantage results from the use of these materials, their high cost makes it unlikely that they will replace $BaSO_4$.

*Chelates.*—Heavy metals with high radiopacity, such as lead and bismuth, form with certain organic acids substances known as chelates. Since bonding is both ionic and coordinate, dissociation is low. This firm combination has led to their use as contrast media in the alimentary tract and even parenterally. However, there is evidence (4) that even these combinations produce the poisoning characteristic of these heavy metals; apparently the high affinity of the chelating acids is exceeded by the affinity of bodily constituents (proteins, enzymes), which are well known to have a high affinity for these metals. It seems unlikely that a useful agent will come from this group.

## Biliary Tract

The introduction of tetraiodophenolphthalein by Graham & Cole (28) marks the beginning of the use of radiopaque diagnostic agents which are dependent upon their disposal by the body after absorption. Subsequently, this compound was supplanted by iodoalphionic acid [$\alpha$-phenyl,$\beta$-(4-hydroxy-3,5-diiodophenyl) propionic acid] (29), not because its excretion in bile was greater or that its toxicity was less, but because its absorption from the alimentary tract was better (30). In this compound, the phenolic hydroxyl

facilitated the introduction of two iodine atoms. An aromatic amino group, permitting the introduction of three iodine atoms, conferring greater radiopacity, gave iopanoic acid [α-ethyl,β-(3-amino-2,4,6-triiodophenyl)-propionic acid] (31). Biliary excretion of these two compounds is about the same, but the greater opacity means better visualization. The toxicity on oral ingestion of iopanoic acid is somewhat uncertain, differing dependent upon whether the acid or the sodium salt is used (32). Apparently, the acid is not well absorbed; residues in the alimentary tract are frequently seen; they occur less often with the Na salt (32). For visualization, the sodium salt is not superior to the acid (32a, 33). Comparative clinical studies indicate that iopanoic acid gives better results and fewer side effects such as nausea, vomiting, diarrhea, and dysuria than does iodoalphionic acid. It was frequently noted that iopanoic acid achieved visualization of the biliary duct without concentration of the material in the gall bladder. Dosage has been increased to achieve this result, but side effects are frequent (33, 34) and one nonfatal 'renal shut down' has been reported (35). The next compound to be introduced, ipodate [β-(3-dimethylamino-methyleneamino-2,4,6-triiodophenyl)-propionic acid] (36) apparently has a rate of excretion and an acute toxicity about equal to that of the previously mentioned substances, but it is well absorbed and may be superior to iopanoic acid, although it also produces side effects. It also has been used in larger doses, which seems to present certain dangers since it is certainly no less toxic than iopanoic acid.

Improved absorption is claimed for Bunamiodyl [Na 3-(3-butyrylamino-2,4,6-triiodophenyl)-2-ethylacrylate]; very little basic information on this compound has been published. The manufacturer's literature claims that it is less toxic to animals than other agents, but the claimed difference is not very great. Comparative clinical trials (37, 38) indicated that Orabilex showed no residues in the bowel and was tolerated in larger doses, so that 4.5 g gave better visualization and fewer side effects than did 3 g of iopanoic acid. However. doses of 4.5 to 22.0 g. of Bunamiodyl have caused at least 12 cases of acute renal failure, five of which were fatal (35, 39–42), revealing diffuse tubular necrosis at post mortem examination. It was concluded that liver disease, jaundice, or underlying renal failure were not necessary prerequisites, that overdosage was the common denominator, and that perhaps some hepatic and renal dysfunction contributed to the results. This compound was removed from the market in February, 1964. It has also been shown to interfere with the excretion of bilirubin (43) and sulfobromophthalein (44), although this may be due, simply, to competition for the excretory mechanism. The desirability of administering these substances in the presence of jaundice or other signs of hepatic deficiency has been questioned. Visualization of the gall bladder is less likely if impaired hepatic function is present as during jaundice (45), after viral hepatitis (46), or in portal cirrhosis without jaundice (47). One death in coma after oral phenobutiodil (48) seems to justify caution in the use of cholecystography in jaundiced patients. All forms of acute liver damage and atrophy and simultaneous hepatic and renal

insufficiency are regarded as contra-indications to the use of iodipamide (49).

The introduction of iodipamic acid (49, 50) made a new departure. This substance [N,N′-adipyl-bis-(3-amino-2,4,6-triiodobenzoic acid)] may be said to be composed of two of the nuclei of acetrizoate (see below) joined together by the dicarboxylic adipic acid. Not absorbed from the alimentary tract its intravenous toxicity ($LD_{60}$ about 10 times that of these other agents) is so low that it may be given by that route. It is excreted in the bile in high concentrations, so that the entire biliary tract is visualized. In a total of 6.2 million injections, 22 mortalities were reported (51).

*Nature of biliary excretion of contrast media.*—The original aim in the use of these agents was to achieve visualization of the gall bladder following oral administration. In general, these substances are weak acids and, with some exceptions, are well absorbed. Since biliary excretion is a slow process, it is necessary that the compounds remain in the body, not be excreted in the urine. This comes about because of their extensive binding to plasma proteins and reabsorption in the renal tubules. They also lack the features leading to renal tubular secretion.

The biliary excretion of these materials is poorly understood, even as to whether such substances are excreted into the bile by the polygonal parenchymal cells or the epithelial cells of the bile ducts (52). The protein binding of these substances, which is high, may contribute to their biliary excretion in that it reduces their urinary excretion, but it is not essential to their biliary excretion, since this occurs with substances not bound to proteins such as PAH (*p*-aminohippurate). Protein binding does not impair biliary excretion, probably because the protein with associated compound freely reaches hepatic cells. There is, presumably, a system which has a greater affinity for the substance, than has plasma protein, to separate it and transfer it into the bile.

Except for iodipamide, concentration of the agent in the gall bladder is important. Normally, little or none of the compound is absorbed there, but this may occur in the diseased gall bladder, contributing to failure of visualization.

The structural features which lead to biliary excretion are not clear. Sperber (53) has pointed out that there appears to be similarity in the requirements for biliary and renal tubular secretion. Unfortunately, much study of biliary secretion has been with compounds such as sulfobromophthalein, which is found in bile, as such and in as many as four different conjugated forms (52).

As for the contrast media, many undergo biotransformation. Iodophthalein in the bile is changed—to what, however, is not clear. Inorganic iodine appears in the urine (54). Iodoalphionic acid appears in bile and urine, as such and as two different glucuronides (55). Of the iodine in the urine, 10 percent may be inorganic (56). Iopanoic acid is present in bile entirely as the glucuronide (57), the biliary excretion of which is much more rapid if it is

given as such, rather than as iopanoic acid (58). This conjugation is important, also, for termination of action, since the glucuronide is not reabsorbed. Iodipamide is apparently excreted in the bile as such. In five of thirteen cases receiving the substance, one fifth of the substance excreted in the urine was as free amino or deacylated compound. Of many experiments in animals, only one rat receiving a subcutaneous injection showed 12 percent of the amount in the urine deacylated (50).

Biliary excretion by active transport without biotransformation may be seen in simpler form with PAH. The dog (59) achieves a bile to plasma ratio of 100 and a maximal excretory rate of 2 μmole per kg per min, as compared with the renal $T_m$ of 5 mmole per kg/min. However, the plasma concentration of PAH for saturation of the hepatic system is about 20 times that for the renal system, requiring a dose, in the dog, of 4.2 μmole per kg. The human dose of iodipamide is 0.1 mmole per kg, so that it is doubtful that saturation is reached, although data are not available. Iodipamide is a choleretic which probably contributes to visualization through greater filling of the biliary tract.



## Urinary System

The development of excretory urography is shown by the following list of compounds (sequenced by year of introduction): (*a*) one iodine atom, sodium iodide (1923), Uroselectan (1929), Methiodal (1931), Iodohippurate (1933); (*b*) two iodine atoms, Iodomethamate (1931), Iodopyracet (1931); and (*c*) three iodine atoms, Acetrizoate (1952), Diatrizoate (1954), Diprotrizoate (1956). The trend that is revealed is an increasing number of iodine atoms, thus increasing radiopacity, and decreasing toxicity (4). The factors leading to successful visualization are discussed in detail elsewhere (3). They include: absence of binding to plasma proteins, so that the compound is free to filter in the glomerulus; confinement to extra-cellular fluids; high rate of renal tubular excretory transport; lack of tubular reabsorption; and minimal osmotic activity.

*Tubular secretion.*—Tubular secretion appears to be an important feature, and since it is frequently stated that the recently-developed agents lack this property, it is discussed in some detail. Inorganic iodide is readily reabsorbed in the tubule, and there is no evidence for its secretion. Uroselectan (5-iodo-2-pyridone-N-acetate) is secreted by the renal tubule of dog and man (60). Methiodal (sodium iodomethanesulfonate) may undergo slight secretion, although this is doubtful (60). Iodohippurate (*o*-iodohippurate) is secreted (60). Iodomethamate (1-methyl-3,5-diiodo-4-pyridone-2,6-dicarboxylate) is poorly secreted (60). Iodopyracet (3,5-diiodo-4-pyridone-N-acetate) is well secreted (60). With Acetrizoate (3-acetamido-2,4,6-triiodobenzoate), study of renal disposal is complicated by its considerable binding to plasma protein. If renal clearance is measured at low plasma concentrations, clearance is readily found to be greater than glomerular filtration rate, indicating tubular secretion (50, 61, 62). If the plasma concentration is raised and protein bind-

ing is ignored, Acetrizoate clearance approaches filtration rate. However, if protein binding is measured by ultrafiltration, preferably of the sample of plasma taken during the period of urine collection, and the results are calculated as transtubular movement as the difference between the amount filtered and the amount excreted, this substance is shown clearly to undergo tubular secretion (27, 63).

The situation is similar with Diatrizoate (3,5-diacetamido-2,4,6-triiodobenzoate). An early study (64) which claimed excretion by filtration only ignored protein binding. Another early study (65) gave results (including ultrafiltration) which on calculation show that, in the dog, from 9 to 45 percent of the amount in the urine reaches it by tubular secretion. Single injection studies in man with Diatrizoate showed that its urinary excretion could not be explained by filtration alone (66). Steady-state experiments in dogs, in which ultrafiltration was done, indicate tubular secretion (27, 63). Perhaps the chief evidence against secretion comes from Woodruff & Malvin (67). Their use of $I^{131}$-labelled compounds leaves them open to criticism, since there is a likelihood of contamination with labelled inorganic iodide. The burden of proof to show that the compound is free from inorganic $I^{131}$ is on the investigator; this evidence is neither provided in the cited paper, nor is adequate quantitative treatment of protein binding. They also performed "stop-flow" experiments at high plasma levels, where interpretation is ambiguous. Further indication of tubular secretion of Diatrizoate is provided by studies of nephrography (see below).

The situation with Diprotrizoate (3,5-dipropionamido-2,4,6-triiodobenzoate) is similar. Steady-state experiments with measurement of protein binding indicate that it is secreted (63).

While tubular secretion of these substances does occur and is important for visualization, the situation in the use of these compounds in excretory urography is described in the following discussion. The dose of compound used is enough to exceed the plasma level at which the tubular secretory mechanism is saturated, beyond which level excretion increases through increased glomerular filtration only. Increased loading may lead to an actual decrease in the urinary concentration of the iodine compound, as a result of the manner of operation of the kidney, in that an increasing osmotic load is excreted in an increasingly larger volume. Actually, this leads to improved visualization, since the volume of the urinary tract (renal pelvis and ureter) increases with increasing urine volume, thus giving a greater depth of layer of absorbing material (3, 68).

To consider the structural features which lead to tubular secretion, if the previous list of compounds is examined, it will be seen that all of the more successful ones (i.e., other than NaI and Methiodal) are amido acids, either structurally or functionally (as the three pyridone derivatives). It is believed that the amido group is functionally important for association with the transport mechanism through hydrogen bonding.

*Nephrography.*—Nephrography designates visualization of the kidney

itself rather than the urinary tract, as in urography. The nature of this procedure, which might be of more practical value than urography, has been explored by Helander (69). His results separate the vascular and excretory phases, showing that the first is unimportant. They leave it unclear as to whether nephrography results from the presence of the medium in the renal tubular cell or in the lumen. Earlier results (70) indicate that nephrography is produced by lowering the arterial pressure or raising the intrapelvic pressure. Since these procedures would reduce or stop glomerular filtration, it seems that nephrography results from accumulation of the opaque medium in the lumen. The importance of tubular secretion for nephrography is indicated by the observation that its production with Iodopyracet, Diatrizoate, or Diprotrizoate was suppressed by the previous administration of PAH.



## Lung

The first successful agents, iodinated vegetable oils, particularly Lipiodol, were condemned (71) because their low viscosity leads to flooding of the alveoli, with retention for many days, and local damage. The addition of sulfanilamide increased viscosity and diagnostic value and reduced alveolar retention. However, this "Visciodol" causes urticaria (72) and produces blood sulfanilamide levels above the usual therapeutic ones, causing methemoglobinemia and cyanosis (73). Absorption of sulfanilamide is greater after intrabronchial administration than after oral ingestion.

A substitute agent is "Dionosil", the propyl ester of Iodopyracet (74). The aqueous suspension is apparently too irritant, locally, for use, but the suspension in arachis oil is apparently suitable. This oil is stated to be less damaging than the iodinated oils, although this has been denied (75).

Recent attempts have been made to use $BaSO_4$ in suspension in a saline solution of sodium carboxymethylcellulose for bronchography. Histological examination reveals that the barium sulfate is retained a long time and is locally damaging (76, 77).

## Toxicity

The classical papers of the Pennsylvania group (78) and other writings (3, 4, 5, 7) permit some general statements to be made. The order of danger of the most common procedures, with mortality figures is: oral cholecystography, six deaths in ? cases; intravenous cholecystography, 22 in 6,200,000; intravenous urography, 99 in 11,546,000; and angiocardiography, 26 in 6824. It is clear that the toxicity is related to the dose, with one big exception (see below). Quantitatively, human and animal toxicity are related in that compounds which are more toxic to animals are also more toxic to man. There is a greater variation in sensitivity among the human population than there is among an animal population, which is not surprising. However, the development of less toxic compounds has not meant a lesser degree of human mortality; in fact, this has remained about the same, emphasizing the principle of usage in maximal tolerated dosage, i.e., the same mortality when a

higher dose, which gives better results, is used. Actually the toxicity of these substances is low, e.g., diatrizoate is given intravenously, 90 g in 1 sec. What other substance may be used in this way? Qualitatively, similar phenomena are seen, leading to prompt death in animals and man; these are: dyspnea, shock, cyanosis, pulmonary edema, and respiratory arrest. A specific suggestion of mechanism has been made. Margolis et al. (79), observed with a fluorescent indicator technique that intra-aortic injection of 70 percent sodium acetrizoate in dogs gave abrupt arrest of the blood flow to the spinal cord with marked blood "sludging", or agglutination of erythrocytes, and impairment of vascular permeability with progressive deterioration of the circulation. Sobin et al. (80) saw similar formation of sausage-like masses of erythrocytes in the human corneal-scleral blood vessels after radiopaque agents. Johnson & Knisely (81) made an extensive study of this phenomenon *in vitro* and *in vivo*, concluding that radiopaque media and blood react to form agglutinated blood cell masses which may plug the smallest vessels. The relative potency of various agents, here, resembled their systemic toxic potency. Read et al. (82, 83, 84) made extensive studies and proposed this mechanism as being important in the high mortality of cardioangiography, showing that radiopaque agents, as well as hypertonic NaCl and glucose, gave red-cell agglutination, causing pulmonary hypertension and death from cor pulmonale. Perfusion of lung and leg showed an increase in vascular resistance to these agglutinated bloods. If perfusion was with saline, plasma, or serum, radiopaque agents had no such effect. It was pointed out that the many so-called "vasoconstrictor" effects of radiopaque agents were actually simply attributable to an increase in resistance to the flow of blood with agglutinated cells. As observed in man, this action in the leg was not prevented by lumbar sympathectomy (85). Subsequent studies (86) confirmed this formation of red blood-cell aggregates and showed that low molecular-weight dextran prevents this effect and approximately doubles the $LD_{50}$ of intravenous diatrizoate in dogs; it may be of clinical value. This protective action of dextran has been confirmed (87) in terms of mortality ratios and prevention of damage to spinal cord and kidney. However, blood sludging as an explanation is discounted on the basis that the responses seen are not characteristic of anoxia, that the sludging of trauma does not engender these reactions, and that polarographic recording of oxygen on the surface of the kidney shows that the period of depression of renal oxygen with acetrizoate is so brief that this, itself, is not likely the cause of renal damage (88). The agglutinative and intravascular clumping action of radiopaque agents has been discounted (89). Also, it is shown that prior infusion of whole blood or saline solution will give protection against diatrizoate in the dog which is equal to that of dextran (90). The hypothesis was advanced that cellular aggregation is not prevented, but that hypervolemia resulting in an increase in central blood volume distends the pulmonary vasculature, allowing the passage of the red cell agglutinates which are evoked by angiographic media,

thus reducing a risk of cor pulmonale arising from sludging and flooding of the capillaries in the lung.

Delayed death and disability from radiopaque agents may result from their effect on the central nervous system (91). Methods of experimental study of this neurotoxicity have been developed and used for the comparative study of agents (79, 92, 93). A double dose increases these effects (94). The blood-brain barrier is ordinarily not readily passed by these substances, which is fortunate in view of their high toxicity as exhibited on intracisternal injection (4). These agents may damage this barrier as they do vascular endothelium (95, 96); this damage may play some role in their toxicity. Damage to the spinal cord may be reduced by previous injection of solutions of glucose or procaine (97).

*Nephrotoxicity.*—Acute renal failure may also be the cause of death from these agents (98, 99). It is important to make a thorough evaluation of renal function before doing pyelography, because risks are great if renal disease exists (100). Myelomatosis is particularly predisposing to renal failure after pyelography (101). An instance of injection of a massive dose of diatrizoate into one renal artery without damage is reported (102). In the dog, equal depression of GFR, RPF, and $T_m$-PAH indicates removal of nephrons from function (103); previous injection of procaine is reported to protect against nephrotoxicity (104).

The big exception to a dose-mortality relationship is the occurrence of alarming or fatal reactions to a very small amount of agent (3). This is a characteristic of "drug allergy" and an increasing emphasis is being laid (78) on this as a cause of death. One difficulty with this explanation is that side reactions appear in patients who have not previously been exposed to the agent. There is also lack of direct evidence for formation of the agent into an antigen. Binding to proteins occurs, but this is an equilibrium phenomenon and not the formation of a new compound. These substances are not regarded as especially reactive; however, many are conjugated which presumably involves passing through an activated state, and other biotransformations may occur (105). One well-established type of reactivity for all these agents is deiodination. This has been directly shown for only a few of them (see above); however, indirect evidence comes from the suppression of thyroid-iodine uptake which they all produce (106), presumably as a result of slow formation of inorganic iodide, only a few milligrams of which are necessary. This raises another possibility, that inorganic iodide, either as contaminant or formed *in vivo*, is the allergen. This would provide a common denominator for all these allergic reactions.

A case has been presented (107) for release of histamine as a source of toxic action of radiopaque agents, but no direct evidence is available.

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