J Forensic Sci, Jan. 1974, Vol. 19, No. 1

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Postmortem Chemistry: Practical Considerations and a Review of the Literature

Determination of postmortem chemical values may be of use in a variety of situations. Results of such studies may demonstrate biochemical abnormalities responsible for death when no autopsy is performed, establish a cause of death where autopsy reveals no significant anatomic pathology, help in the evaluation of the physiological effects of recognizable anatomic lesions, and assist in estimating the time of death.

With the development of automation in the hospital laboratory, ease of performance and low cost makes routine examination of postmortem blood and body fluids both practical and desirable. A sufficient body of published knowledge has now been accumulated to enable an investigator to interpret postmortem values for a wide variety of substances. It has been found that some biochemical materials remain remarkably stable in the blood after death while others show varying degrees of change. When change occurs, the alterations follow predictable patterns for certain substances while being totally erratic for others.

Where marked changes from antemortem values occur in postmortem blood, other body fluids have been examined in an attempt to get a more accurate estimate of possible antemortem abnormalities. Cerebrospinal fluid was first studied and found to be of value for certain abnormalities. However, collection of cerebrospinal fluid is inconvenient and it may be difficult to obtain fluid free of blood or other contaminants. Furthermore, changes in cerebrospinal fluid occur fairly rapidly and tend to be erratic.

To obviate the problems associated with cerebrospinal fluid, there has been an increasing use of vitreous humor for chemical analysis. The eye is isolated and well protected anatomically so that vitreous humor is usually preserved despite serious trauma to the head and is much less subject to contamination or putrefactive change than either blood or cerebrospinal fluid. Most importantly, it has been found that chemical changes for many substances occur much more slowly in vitreous humor than in the blood or cerebrospinal fluid. With care, approximately 2 ml of crystal-clear fluid can be obtained from each eye. Material from one eye is sufficient for determination of electrolytes, urea nitrogen, and glucose, leaving material from the second eye for other constituents, duplicate analyses, or toxicological procedures.

This article is a compendium of the available data in the English literature covering postmortem chemistry of blood, cerebrospinal fluid, and vitreous humor. Each type of fluid is discussed independently to provide the reader easy availability to general informa-

Received for publication 20 April 1973; accepted for publication 21 May 1973.

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tion and references for any particular substance in any of the fluids discussed. The use of the various fluids in evaluating preexistent disease or in helping to solve other forensic problems is discussed. A few comments are made on the use of vitreous humor for toxicological analyses.

The information provided deals only with changes in the early postmortem period, which is defined as the interval between death and the onset of intravascular hemolysis, rather than as any particular number of hours.

Blood

Carbohydrates

Glucose—The first significant work with forensic application in the English literature was by Hamilton-Paterson and Johnson [*27*][2] in 1940. They demonstrated that glycolysis occurred in postmortem blood from peripheral vessels, while blood from the right atrium commonly had high glucose values from glycogenolysis. They further showed that extremital blood from diabetics had high glucose levels and that glycolysis in such cadavers occurred much more slowly than usual.

In 1941 Hill [*29*] wrote a classic paper proving three significant points by animal experiments. First he established that the elevated blood glucose usually found in the right atrium came from glycogenolysis in the liver; second, he established that glycolysis occurred at the same rate in vitro as in vivo (approximately 12.8 mg/dl per hour); and, third, he proved that asphyxia would produce a marked rise in terminal blood sugar. Referring then to human postmortem studies he listed nondiabetic conditions associated with significant terminal elevations of glucose including carbon monoxide poisoning (values as high as 336 mg/dl), increased intracranial pressure (one example had 560 mg/dl glucose in postmortem extremital blood), and obstruction of the upper respiratory tract (one patient who died of hanging revealed a postmortem glucose of 608 mg/dl). In no case was the peripheral hyperglycemia over 650 mg/dl in any condition other than diabetes.

Tonge and Wannan [*79*] reestablished in 1949 that there were substances other than glucose producing reactions in the usual tests, and showed that postmortem blood contained considerable quantities of non-fermentable reducing substances. They felt that this accounted for the fact that by routine laboratory methods one almost never finds a zero value for glucose, no matter from where a specimen is obtained or how long it is obtained after death. In contrast to Hill's experimental work, the rates of glycolysis in vivo and vitro were found to be quite different, so that appreciable levels of true glucose were detectable in some bodies even as long as 60 h after death in which the terminal blood glucose was assumed to be normal. Their paper included one attempt at glucose deter-termination on a body with advanced putrefaction in which the total reducing substances were over 2000 mg/dl but true glucose was absent. Having studied a wide variety of cases, they substantiated Hill's observations of postmortem hyperglycemia in conditions other than diabetes. Elevated levels were found in two cases of hanging and two cases of acute coronary occlusion (one with cerebral hemorrhage and one due to electrocution). However, in none of these cases did the glucose level exceed 300 mg/dl. Of five diabetics studied, only one had a value less than 400 mg/dl.

More recent publications [*20*, *61*] only support previous work and offer nothing new.

Lactic Acid—Jetter [*35*] studied 20 cases and found very small amounts of lactic acid normally in both plasma and erythrocytes during life (circa 1 mEq/l). At 1 h postmortem,

[2] Due to the nature of this paper, references are listed in alphabetical order rather than the order in which they appear in the text.

the values increased prominently (circa 20 mEq/l). There was a progressive increase so that at 12 to 24 h after death, the lactic acid values were 50 to 75-fold higher than normal antemortem concentrations.

Nitrogenous Compounds

Blood Urea Nitrogen—Sander [*63*] in 1923 established the prolonged stability of urea in blood after it has been removed from the body. Paul [*56*] in 1925 first proved the stability of urea in the body by drawing samples from the same cadaver at varying postmortem intervals, and showing that they remained constant in value between specimens drawn as early as ½ h after death to some taken as late as two days postmortem. This was true whether the urea nitrogen was in normal range or markedly elevated.

Subsequent work by Pucher and Burd [*60*], Polayes et al [*58*], and Naumann [*48*] suggested an increase in urea nitrogen after death. However, more recent work by Levonen et al [*38*], Jenkins [*32*], Jensen [*33*], Fekete and Kerenyi [*20*], and Coe [*13*] have all established that urea nitrogen concentrations in the serum postmortem closely approximate those in the terminal antemortem blood, irrespective of the procedure used (urease or the carbomido-diacetyl method of Skeggs). This was found to be true for all levels of urea concentration from normal individuals to those showing severe uremia. Fekete and Kerenyi found mean postmortem blood urea nitrogens in individuals dying suddenly to average 15.5 mg/dl. Coe in a similar series had an average postmortem concentration of 13.8 mg/dl. In contrast, Fekete and Kerenyi found in hospital patients dying without evidence of kidney disease, an average postmortem serum urea nitrogen of 47.4 mg/dl. They felt, as does the present author, that the apparent postmortem elevation of blood urea nitrogen reported by the earlier workers really represented agonal changes in hospital patients where the antemortem concentrations were frequently obtained several days prior to death.

Substantiating Paul's earlier work, Levonen et al [*38*] and Coe [*13*] have both demonstrated how extremely stable urea is in the body postmortem. Coe found it to be the most stable of any substance studied, showing in the majority of cases less than 2 mg/dl variation in specimens obtained over 100 h apart from the same cadaver.

Creatinine—In 1923 Sanders [*63*] pointed out that creatinine, similar to urea, was remarkably stable in postmortem blood remaining constant in specimens stored for two weeks. Paul [*56*] found that creatinine remained stable in bodies from which two samples of blood were drawn at different postmortem intervals. This was substantiated by Polayes et al [*58*], Naumann [*48*], Hamilton [*26*], Jenkins [*32*], and Jensen [*33*]. The remarkable stability of creatinine in postmortem specimens was best established by Levonen et al [*38*] who found levels of creatinine to show an average increase of only 0.35 mg/dl in specimens taken 96 h apart from the same cadaver. Several authors point out that creatinine levels are proportionately closer to known antemortem levels than urea nitrogen values from the same individual. In some cases this is undoubtedly due to the fact that creatinine seems less subject to increase from conditions causing prerenal elevations in terminal serum urea concentration.

Nonprotein Nitrogen—In contrast to urea nitrogen and creatinine, Sanders [*63*] demonstrated that the concentration of nonprotein nitrogen rose in stored blood and that the increase could not be accounted for by an increase in ammonia and amino acid content. Sanders's observations on stored blood were substantiated in specimens drawn from cadavers at varying postmortem intervals by Hamilton-Paterson and Johnson [*27*] and by Schleyer [*65*]. In individuals where antemortem retention could be safely ruled out,

Schleyer found the increase in plasma NPN values were sufficiently predictable that values of less than 50 mg/dl could be expected to be derived from bodies that were dead for less than 12 h.

Amino Acid Nitrogen—Pucher and Burd [*60*] demonstrated a sharp postmortem increase of the free amino acid nitrogen concentration in the blood caused by enzymatic breakdown of proteins. This was further developed by Schleyer [*65*]. Values less than 14 mg/dl were usually found in periods under 10 h postmortem. Concentrations continue to increase until enzyme exhaustion, with values frequently over 30 mg/dl by 48 h after death.

Ammonia—Schleyer [*65*] found concentrations of ammonia in plasma from peripheral veins to be in the 1–3 mg/dl range by Conway's method for several hours after death. There was a sharp rise after the initial 8-h period.

Uric Acid—Pucher and Burd [*60*] found an average uric acid of 6.2 mg/dl in ten individuals 8 h postmortem. Naumann [*48*] had similar results with an average serum value of 5.5 mg/dl 6 h after death.

Other Organic Compounds

Cholesterol and Lipids—Naumann [*49*], Enticknap [*17*], and others have all demonstrated that the total serum cholesterol remains in the normal range postmortem. The average for Naumann's series was slightly elevated above the average of normal while Enticknap showed cholesterols slightly reduced. Naumann found the cholesterol esters to be markedly reduced by an esterase active in postmortem blood. He felt that esters could not be used as a reliable postmortem test of hepatic function.

Enticknap [*17*, *18*] showed that other lipid substances, such as total serum fatty acids, total lipoproteins, and beta lipoproteins, were all markedly stable postmortem showing little reduction due to autolysis (.5 percent/h or less).

Bilirubin—Naumann [*49*] felt that postmortem bilirubin values were consistent with antemortem values. However, he gives an average of only twelve cases with an average postmortem interval of 10½ h in which the concentration for total bilirubin is 0.1 mg/dl higher than the upper limit of his normal antemortem range. Coe [*13*] found in a study of 94 individuals with normal antemortem bilirubins, that there was a small but definite increase in average bilirubin concentration with increasing postmortem time (0.2 mg/dl in 2 h, 0.7 mg/dl in 20 h). However, in icteric individuals bilirubin concentrations were nearly identical before and after death, enabling one to determine the degree of antemortem jaundice from postmortem values.

Protein—Naumann [*49*] in 1956 reported that total protein and albumin/globulin ratios in normal individuals determined by chemical means were in the range found for antemortem specimens. Coe [*12*] showed that total protein by Autoanalyzer using the biuret method reveals no significant change between antemortem and postmortem values. Albumin decreased an average of 4 percent.

Schlang and Davis [*64*] presented the first detailed report on electrophoresis of postmortem serums. They demonstrated that the usual serum proteins were readily identifiable and that an increase in the beta globulins was a fairly constant finding. Robinson and Kellenberger [*62*] in 1962 gave a much more detailed study of paper electrophoretic analysis of antemortem and postmortem serum. In 20 cases they found that the overall shape of the postmortem patterns differed greatly from the antemortem in only two instances, both of which manifested a high broad peak in the beta region. These were believed to be due to hemolysis. In comparing all antemortem and postmortem specimens,

there was a fall in the albumin with unchanged alpha 1 and alpha 2 globulins, an increased beta globulin, and slightly increased gamma globulins. The character of the increase in the gamma globulins was nonspecific and was not likely to be confused with a monoclonal peak from myeloma. Using cellulose acetate, Coe [*12*] compared antemortem and postmortem electrophoretic tracings on 18 people and found good correlation except when there was hemolysis. In 16 cases with no hemolysis a 4 percent fall in albumin and a 5 percent rise in beta globulin were found. Other fractions remained essentially unchanged.

Both Brazinsky and Kellenberger [*5*] and McCormick [*43*] studied immunolobulins and found good general correlation between antemortem and postmortem specimens.

Enzymes

Acid phosphatase—Enticknap [*16*] showed that there was a marked postmortem elevation in the acid phosphatase with values over 20 times normal antemortem concentrations by 48 h after death.

Alkaline phosphatase—In 1956 Naumann [*49*] pointed out that alkaline phosphatase became elevated postmortem. He found an average concentration of 5.3 Bodansky units in 14 cases 10½ h after death (normal antemortem range, 1.5–4 Bodansky units). Enticknap [*16*] showed an increase in the alkaline phosphatase using the King Armstrong procedure through the first 48 h postmortem. The average high value at the end of two days was approximately ten times the normal antemortem value. Coe's [*13*] work is in agreement (values doubled in 8 h, tripled in 18 h).

Amylase—Enticknap [*16*] demonstrated that amylase becomes elevated after death reaching a high value on the second day with values three to four times those found antemortem.

Glutamic oxalic transaminase (AST) and lactic dehydrogenase (LH)—Enticknap [*16*] showed a striking progressive postmortem increase in concentration of both enzymes. The increase in concentration was roughly linear with time for the first 60 h after death so that a crude estimation of the postmortem interval was possible.

Esterase including cholinesterase (CE)—Petty et al [*57*] studied the true (red blood cell) blood cholinesterase from 130 postmortem subjects and found an average of 1.47 micromoles of acetyl-choline utilized. There was no significant difference based on color, sex, age, or cause of death. The true cholinesterase remained stable. No significant difference was found between refrigerated and nonrefrigerated samples and no significant decrease in activity was noted in samples periodically analyzed up to three weeks after death.

Moraru et al [*44*] reported on total cholinesterase (red blood cell and pseudocholinesterase) using Fleisher and Pope's colorimetric method. This method was performed in 40 cases, with blood collected from 10 h to three days after death. They demonstrated that total cholinesterase was stable for ten days in refrigerated samples, but that the total cholinesterase displayed great individual variation. In deaths preceded by a long period of illness, the cholinesterase concentrations were found to be much lower (0.59 ± 0.26 micromoles/ml) when compared to deaths of persons dying suddenly and traumatically (1.34 ±0.47 micromoles/ml).

In 1972 Arnason and Bjarnason [*3*] studied total serum esterase by starch gel electrophoresis on postmortem serums obtained from ¼ to 720 h after death. Some samples were taken from the same body at intervals. Six esterase fractions can be demonstrated in sera from living individuals but several fractions disappear in postmortem serum; one fraction becomes stronger, continuing to increase in strength for at least 100 h after death; and at least one new fraction develops that is not found in serum from live patients. The authors believe proteolytic enzymes are the cause of these changes.

Hormones

Cortisol—Finlayson [*23*] in 1965 established that postmortem cortisol concentrations were the same as those during life and remained stable for at least 18 h after death.

Adrenalin and noradrenalin—Lund [*41*] studied the postmortem catecholamines in the blood of normal individuals. He found the concentrations higher than concentrations found in the blood of living patients with pheochromacytoma, and as high as in bloods from cases of accidental fatal adrenalin poisoning. There was a significant difference in the adrenalin content of blood from cases of violent (27 μg/l) and natural (55 μg/l) sudden death. The difference is presumed to be due to a difference in duration of the occurrence of death with the lowest adrenalin concentration found in the most rapid deaths.

Thyroxin and thyroid stimulating hormone—Coe [*11*] found that T_4 values tend to fall after death. The rate of fall is individual and erratic, causing postmortem concentrations in some cases without thyroid disease to be in the range of hypothyroid individuals. In contrast, TSH values showed only minor variations and remained in the normal range for one to two days after death.

Insulin—Postmortem insulin levels are under investigation by Sturner [*78*]. While he and Putnam primarily studied concentrations found in the bile [*72*], he was also determining serum levels and in 25 cases found serum concentrations to vary from 0–200 microunits/ml. In 22 of the 25 cases, insulin levels were under 100 microunits/ml. The three cases with values between 100 and 200 microunits/ml were diabetics who used exogenous insulin in their treatment. All bloods were obtained from the heart.

In 1972 Lindquist [*40*] demonstrated that postmortem serum insulin values are higher than those of healthy individuals. Furthermore, he showed that in the same body there can be great variation in concentration of insulin depending on the source of the serum. In 43 non-diabetic individuals who died from a variety of natural and traumatic conditions, insulin concentrations in blood obtained from the right atrium averaged 187 microunits/ml (range 7–590), compared to 23 microunits/ml (range 5–55) in blood taken from the femoral vein. In one individual who died from an overdose of a tricyclic antidepressant, 2400 microunits of insulin/ml of serum were found in the right atrium and 179 microunits/ml in serum from the femoral vein.

Electrolytes

Sodium—The only direct reference in the English literature to postmortem sodium is that of Jetter [*35*]. He found that the serum sodium remained constant during the first 12 h postmortem when a somewhat inconclusive decrease began. Several recent articles concerned with electrolyte changes after drowning have indirectly shown that the sodium values decrease postmortem. Coe [*13*], in a more detailed study, has demonstrated that the sodium begins to decrease immediately after death but that the rate of decrease shows a great deal of individual variation. Least squares regression analysis of a large group of observations revealed the average rate of fall to be 0.9 mEq/l per hour.

Chloride—Jetter [*35*] reported that there was a decrease in plasma chloride through an intracellular shift with an average concentration in the range of 80–90 mEq/l 24 h after death. Schleyer [*65*] and other European workers have substantiated the plasma chloride decrease and report it to be at the rate of approximately 0.25–1 mEq/l per hour. In least squares regression analysis of a large series Coe [*13*] found the rate of fall to be 0.95 mEq/l.

Potassium—Jetter [*35*] pointed out that within 1 h after death there was a marked increase in potassium with values up to 18 mEq/l followed by further, although gradual, increase in the levels. It has been shown by extensive work in blood banks and elsewhere

[*81*] that the release of potassium from the cells occurs so rapidly after death that it makes evaluation of potassium metabolism impossible by any known method.

Calcium—Jetter [*35*] states that calcium remains constant in the early postmortem period and Naumann [*54*] agrees. While the method of calcium determination was not reported by Jetter, it was probably the Clark and Collip procedure used by Naumann. This procedure is specific for calcium. In contrast the Autoanalyzer procedure using cresolphthalein complexone has interference from magnesium causing an apparent rise in postmortem calcium [*13*].

Phosphorus—Jetter [*35*] reported an increase of inorganic phosphorus in serum occurring as early as 1 h postmortem and reaching levels of 20 mEq/l 18 h after death. Organic phosphorus also showed an increase. This is substantiated by Schleyer [*65*].

Magnesium—Jetter [*35*] points out that tissue magnesium is high in contrast to plasma levels in the living individual and states that during the early postmortem period, tissue cell integrity seems to be maintained so that there is only a mild increase in the plasma magnesium. When hemolysis occurs, however, plasma magnesium increases rapidly so that eventually levels of 20–30 mEq/l were found in the plasma. Coe's [*7*, *13*] investigation with calcium determinations by cresolphthaline complexone suggests that magnesium begins to leave the cell before significant hemolysis occurs, causing a false apparent elevation in calcium.

Carbon Dioxide Combining Power and Carbon Dioxide Content—Jetter [*35*] showed a marked rapid decrease in the carbon dioxide combining power, which he thought was probably due to the marked postmortem production of lactic acid with immobilization of base as sodium lactate. Carbon dioxide content, however, remained constant. In contrast, Coe [*13*] found an apparent exponential decrease in carbon dioxide content which he felt to be a technical artefact of the Autoanalyzer procedure. The decline in serum values probably reflected the fall in carbon dioxide combining power.

Blood Gases

Oxygen Tension—Patrick [*55*] in 1969 gave the following results on postmortem oxygen tension for 28 cases. The specimens were obtained an average of 6 h after death.

Cause of Death	Number	Mean PO_2
Sudden infant death	7	13.7
Sudden "explained" death	6	21.0
Random autopsy series	15	24.8

He further states that in the autopsy series were individuals who had been dead for 24 h in whom the oxygen tensions were in high as 45.

Cerebrospinal Fluid

Carbohydrates

Glucose—Hamilton-Paterson and Johnson [*27*] first showed in 1940 that the glucose levels in cerebrospinal fluid were high in individuals with hyperglycemia. They demonstrated that glycolysis occurred, but progressed at a slower rate than in normal subjects. In 1950 Naumann [*48*] reported on postmortem glucose values in the cerebrospinal fluid and felt them to be a much better indicator of diabetes than peripheral blood. In non-

diabetics the spinal fluid glucose remained below 200 mg/dl, even in asphyxial deaths of the type found by Hill [*29*] and others to produce a terminal hyperglycemia. Values over 200 mg/dl, especially when accompanied by positive tests for acetone, were considered to be diagnostic of uncontrolled diabetes.

Fekete and Kerenyi [*20*] reported that cerebrospinal fluid glucose fell very rapidly after death even when postmortem hyperglycemia existed. Spinal fluid values over 150 mg/dl were thought to signify antemortem hyperglycemia. Diabetics as a group had still higher sugar levels (an average of 212 mg/dl). They further stated that antemortem hypoglycemia could not be recognized by postmortem cerebrospinal fluid sugar determinations.

Lactic Acid—Schleyer [*65*] reports that the concentration of lactic acid in cerebrospinal fluid will increase after death. There is a sharp and fairly regular rise up to the tenth hour, with a definite slackening of the increase and a great range of variability thereafter. The determinations were made with the hope that the increases in lactic acid could be correlated with the postmortem interval but the conclusion was that the method was not reliable.

Nitrogenous Compounds

Urea—Pucher and Burd [*60*] first reported on urea in postmortem spinal fluid and found it averaged 73 percent of the serum concentration, but Naumann [*48*] reported in 1949 that cerebrospinal fluid levels were somewhat higher than normal antemortem blood levels. Nevertheless, Naumann felt the cerebrospinal fluid concentrations more closely reflected antemortem serum concentrations than levels obtained from the study of postmortem blood. Jenkins [32] reported in 1952 that the postmortem cerebrospinal fluid urea levels were the same as, or somewhat lower than, the blood levels at death. He felt that the spinal fluid level could be taken as a reliable guide of the state of antemortem urea retention. Jensen [*33*] reported similar results and thought there was no overlap between values obtained from normal individuals, even with prerenal nitrogen retention, and individuals with true clinical uremia. In 1965 Fekete and Kerenyi [*20*] reported that cerebrospinal fluid urea concentrations were constant for the first 36 h after death, irrespective of the time of collection, and the upper limit of postmortem normal was 25–30 mg/dl.

Nonprotein Nitrogen—Hamilton-Paterson and Johnson [*27*] showed there is a progressive increase in nonprotein nitrogen with increasing time after death. This increase has been verified by Schleyer [*65*], who demonstrated that there was a generally arithmetic rise in the concentration during the first 30 h postmortem, following which the rate of rise began to decrease. No values exceeding 80 mg/dl in the cisternal fluid could be used for evaluating the postmortem interval.

Creatinine—Pucher and Burd [*60*] showed an 8-h average postmortem spinal fluid creatinine of 1.6 mg/dl in ten individuals. Bolliger and Carrodus [*4*] in 1938 demonstrated that cerebrospinal fluid creatinine concentrations reflected the blood concentrations and remained constant after death. This was substantiated by Naumann [*48*] and Jensen [*33*], both of whom felt that creatinine was the best method to analyze for evaluation of kidney function. Naumann thought that mild degrees of prerenal uremia produced no significant increase in creatinine levels.

Amino Acid Nitrogen—In 1925 Pucher and Burd [*60*] first described the postmortem increase of free amino acid nitrogen due to the enzymatic breakdown of proteins. This fact has been substantiated by several workers and most extensively studied by Schourup and Schleyer [*65*]. These investigators have demonstrated a general arithmetic rise in

values with increasing time and felt the procedure to be of some use in estimating the postmortem interval for the first 20 h after death.

Ammonia—Ozsvath is quoted by Schleyer [*65*] as having reported a generally linear rise of cerebrospinal fluid ammonia with increasing time after death. Concentrations of less than 1 mg/dl were found immediately after death but rose to over 8 mg/dl by 60 h postmortem.

Uric Acid and Xanthine—Pucher and Burd [*60*] found spinal fluid uric acid to be 2.6 mg/dl for ten individuals 8 h postmortem. Average uric acid concentrations on nine individuals increased from 1.7 to 2.6 mg/dl in 6 h after death according to Naumann [*48*]. Praetorius et al [*59*] reported a 100-fold increase in xanthine and hypoxanthine after death, measured in terms of uric acid production. The initial concentration of the xanthine and hypoxanthine was found to range between 0.25 to 1.50 micrograms/ml.

Creatine—Bolliger and Carrodus [*4*] demonstrated that in contrast to creatinine, creatine definitely rose in the cerebrospinal fluid following death. Naumann [*48*] showed concentrations increased progressively with increasing postmortem time, but did not attempt to use it as a method of determining the postmortem interval. Schleyer [*65*] substantiated Naumann's work and felt it could serve as a rough indicator of the time between death and the withdrawal of the sample.

Other Organic Compounds

Urobilinogen—Naumann [*46*] demonstrated that urobilinogen will diffuse from blood to cerebrospinal fluid whenever the blood level is high and the cerebrospinal fluid-blood barrier is disturbed. There was a rough parallelism between cerebrospinal fluid and urinary urobilinogen.

Bilirubin—Naumann and Young [*53*] found in a study of 43 icteric individuals, that total bilirubin was demonstrable in the cerebrospinal fluid by the method of Malloy and Evelyn in a 1:35 ratio of spinal fluid to serum. Direct acting bilirubin was found to give a cerebrospinal fluid:serum ratio of 1:45.

Electrolytes

Naumann [*50*] demonstrated that the concentration of many electrolytes changed significantly after death but not with a sufficiently close correlation to time to serve as a means of determining the postmortem interval. Values found for anions and cations in 131 cases an average 10½ h after death are compared to normal antemortem values below:

	Postmortem mEq/l	Antemortem mEq/l
Na	127	143
Cl	113	125
K	21	2.9
HCO_3	9.4	2.6
Ca	2.4	2.5
Mg	2.9	2.0
P	5.2	0.8

Potassium—Mason et al [*42*] first noted the postmortem rise in cerebrospinal fluid potassium. They felt the concentration increased in proportion to the logarithm of the time up to 70 h after death. Naumann [*50*] thought that the potassium increase was predictable only on a statistical basis and could not be used for prediction in an individual

case. Fraschini et al [24] also found increasing potassium levels with increasing time after death, and felt that their finding might have forensic implications. Murray and Hordynsky [*45*], analyzing cerebrospinal fluid in 46 hospital cadavers, found the average rate of potassium increase to be constant in relation to time of death and the temperature of the body. However, there is much individual variation apparent in their graphs and Schleyer [*65*] later demonstrated that beyond the twentieth hour after death, time estimates become completely unreliable.

Vitreous Humor

In contrast to blood and cerebrospinal fluid, there are no normal values for vitreous humor available from clinical studies. Presumed normals must be obtained from extrapolation of postmortem values, experimental studies on animals, and a few studies of questionable value on enucleated eyes (questionable since enucleation is never carried out in the absence of disease or injury that will distort the chemical constituents present). While the animal experiments can be carefully controlled, they demonstrate considerable variation in concentrations of chemical constituents between the different species studied, and conclusions drawn from them are frequently at odds with data obtained from postmortem studies on human specimens. For these reasons the subsequent section will report only studies on human postmortem material.

Carbohydrates

Glucose—Naumann [*52*], Sturner and Gantner [*68*], and Leahy and Farber [*36*] felt the normal vitreous glucose to be approximately one half the serum level and to be stable. However, in a study in which vitreous was drawn from the same individual at varying intervals after death, Coe [*6*] demonstrated that the initial values were approximately 85 percent of the serum level by ferricyanide reduction, and then decreased after death. The postmortem decrease could be marked and was very precipitous in individual cases. As a consequence very low concentrations of vitreous glucose wihich Sturner and Gantner [*68*] felt to be indicative of hypoglycemia (25 mg/dl) were proven to be simply a result of postmortem change. Coe thought it impossible to make a diagnosis of hypoglycemia except under very limited circumstances. All authors have found, however, that study of the vitreous glucose is valuable for determining antemortem hyperglycemia and, together with a test for ketone bodies in the vitreous, it can be used for determining diabetic acidosis.

Lactic Acid—Jaffe [*31*] found the concentration of lactic acid increased after death from an initial value of 80 to 160 mg/dl to 210–260 mg/dl after 20 h.

Pyruvic Acid—Jaffe [*31*] reported that the concentration of pyruvic acid decreased rapidly after death from 2 to 3 mg/dl to 0.1 to 0.2 mg/dl after 10 h.

Ascorbic Acid—Jaffe [*31*] found that vitreous fluid contained the highest concentration of ascorbic acid in the body, with the levels falling slowly within the first 20 h. The initial concentrations obtained during the first hour postmortem ranged from 19–38 mg/dl. Gantner et al [*25*], studying materials from 32 cases, found the baseline levels in them to be extremely variable, increasing from 2.0–22.0 mg/dl. Samples placed in sequence showed a tendency toward an increase in ascorbic acid concentration during the first 5 h, after which the values slowly declined.

Nitrogenous Compounds

Urea—Naumann [*52*] thought the postmortem urea of the vitreous to be moderately elevated. His study, however, was carried out on hospital patients who probably had a

terminal elevation of the blood urea nitrogen. In contrast to Naumann's work, Leahy and Farber [*36*] found the vitreous urea to be in a normal range for individuals dying suddenly or with a known terminal normal antermortem blood urea nitrogen. Coe [*6*] found the vitreous urea nitrogen to be in normal range for normal individuals, and to parallel the blood urea nitrogen over all ranges of urea retention. Furthermore, it was by far the most stable of all postmortem constituents studied showing in over 90 percent of the cases a variation of less than 3 mg/dl between specimens drawn over 100 h apart.

Creatinine—Naumann [*52*] found vitreous creatinine to be normal after death as did Leahy and Farber [*36*]. Both of these investigators found the vitreous levels to be slightly lower than serum levels. Naumann found an average postmortem vitreous creatinine of 1.2 mg/dl compared to an average serum creatinine of 1.5 mg/dl in the same individuals. Leahy and Farber showed that in five individuals with terminally elevated blood and vitreous urea nitrogen, the vitreous creatinines remained at normal levels.

Nonprotein Nitrogen—Jaffe [*31*], in a study of 13 cases, found the concentrations of nonprotein nitrogen to increase erratically with no consistent pattern detectable.

Uric Acid—No author makes any statements concerning vitreous uric acid, but Sturner et al [*74*] present concentrations in 44 individuals who died from a variety of traumatic and natural causes in which normal serum uric acid levels would be expected. Vitreous uric acid values varied from 0.7–3.0 mg/dl. In 22 cases having an average postmortem interval of 4.0 h, the average uric acid was 1.3 mg/dl. In the remaining 22 individuals with an average postmortem interval of 16.5 h, the average uric acid was 1.5 mg/dl.

Other Organic Compounds

Enzymes—Leahy and Farber [*36*] ran tests for lactic dehydrogenase, glutamic oxalic transaminase, and glutamic pyruvic transaminase. In all cases measurable activity was minimal and often absent. In no case was there any apparent correlation with either normal or elevated antemortem serum concentrations of these enzymes. Coe [*6*] found values for vitreous glutamic oxalic transaminase extremely variable, with values from 12–205 units obtained. The values bore no relation to antemortem blood values or to any pathologic condition in the eye or in the body as a whole.

Proteins and Amino Acids—The concentration of soluble protein in vitreous humor is 40–80 mg/dl in man. Vilstrup and Kornerup [*80*], by paper electrophoresis, revealed the protein in purified sample of human vitreous body to be computed of albumin and globulin in a ratio of 46 : 54, as compared to normal human serum giving a ratio of 74:26 in control tests. Cooper et al [*14*], by immunochemical analysis of the vitreous, demonstrated a large number of serum proteins to be present. They found one protein in the alpha globulin fraction in concentrations higher than in the serum itself, which suggested a possible selectivity on the part of human vitreous for serum proteins. Human vitreous was also found to contain a number of antigens not shared with serum, of which the origin, chemical composition, and localization were not determined. Finally, Erdei and Vass [*19*] demonstrated the present of free aminoacids in the vitreous by paper chromatography and found them to be identical to aminoacids liberated from the vitreous by the enzymatic action of elastase. It was their tentative conclusion that autolysis due to the effect of proteolytic enzymes was responsible for the presence of the free aminoacids in the vitreous body.

Bilirubin—Coe [*6*] found no evidence of vitreous bilirubin when using the Jendrassik and Grof procedure, even in individuals with jaundice. However, Naumann and Young

[53] using the classical Malloy and Evelyn method, found that bilirubin does enter the vitreous in small amounts. In 43 icteric individuals with an average serum concentration of 8.6 mg/dl, the vitreous showed bilirubin values of 0–0.48 mg/dl with an average of 0.04 mg/dl. This gives a vitreous : serum ratio of 1 : 220 for total bilirubin, while the ratio for direct acting bilirubin was 1 : 480.

Electrolytes

Sodium—Naumann [52] found vitreous sodium values to vary from 118–154 mEq/l with an average of 144 mEq/l. Leahy and Farber [36], in a smaller series, had a range of 128–158 mEq/l and substantiated the postmortem stability of this substance. In two patients with antermortem hypernatremia they found the vitreous sodium concentration to be significantly elevated. Similarly, Coe [6] found that the sodium was extremely stable in the early postmortem interval and had a much narrower range of normals on 145 individuals, where values were found to vary from 135–151 mEq/l with an average of 143 mEq/l. Coe, studying hospital patients with both hyponatremia and hypernatremia, found that vitreous values greater than 155 mEq/l or less than 130 mEq/l reflected significant serum deviations which had been found to exist prior to death.

Chloride—Naumann [52] found an average vitreous chloride of 114 mEq/l. Leahy and Farber [36] reported their normal range to vary from 108–142 mEq/l for 39 patients with normal antemortem serum chloride values. Coe [6] found chlorides to range from 104–132 mEq/l with an average of 120 mEq/l. As was true with sodium, the concentrations remained almost constant for an average of 18 h postmortem. Sturner and Dempsey [75], reporting on vitreous values of 44 infants who died suddenly and unexpectedly, found an average normal of 120 mEq/l. Chlorides below 105 mEq/l or over 135 mEq/l are felt to reflect antemortem hypochloremia and hyperchloremia.

Carbon Dioxide Content—Coe [6] found the carbon dioxide content as measured by the Autoanalyzer to vary from 4–27 mEq/l, with an average value of 15 mEq/l. This was suprisingly stable, indicating a fall of only 2 mEq/l in 15½ h.

Calcium—Naumann [52] found an average concentration of 7.2 mg/dl in his series of 211 cases, with an average postmortem interval of 9 h. Coe [6] found calcium concentrations remained constant during the early postmortem interval, and varied from 6.0 to 8.4 mg/dl with an average of 6.8 mg/dl. Coe found in several hospital patients who had terminal hypocalcemia, that the vitreous calcium was within normal limits. Sturner et al [74] also reported a similar range of normal vitreous calcium values, but found a depression of calcium concentration in several traumatic cases for which no explanation was apparent.

Magnesium—There has been no extensive investigation of vitreous magnesium. The only report available is that of Sturner [76], who found a range of 1.5–2.5 mEq/l of magnesium in a series of 24 adults and concentrations of 2.0–3.9 mEq/l in a series of 20 infants, using atomic absorption spectrometry. The causes of death and postmortem intervals in these cases were not provided.

Phosphorus—Naumann [52] reported inorganic phosphorus to vary from 0.1–3.3 mEq/l with an average concentration of 1.2 mEq/l.

Iodine—DeJorge and Jose [15] found the vitreous iodine in five postmortem enucleated adult normal eyes to vary from 5.1–5.9 μg/100 g of fresh tissue, with a mean value of 5.44 μg/100 grams.

Potassium—Jaffe [31] first noted that potassium increased in the vitreous in a regular fashion. This was later substantiated by Adelson et al [1], Hanson et al [28], Hughes

[30], Lie [39], Sturner [67], Sturner and Gantner [69], and Coe [6]. Adelson et al established that the rise was arithmetic for any group of patients and independent of environmental factors. The average rate of rise was 0.17 mEq/h. Other investigators substantiated their work, but there was variation in the degree of correlation between the vitreous potassium concentration and the postmortem interval. Sturner, Gantner, and Lie found such close correlations that they believed the method could be used with a confidence limit of ±5 h. Adelson et al, Hughes, Hanson et al, and Coe all found such individual variation that the confidence limit of the method exceeded ±10 h on the first day after death. Hanson et al and Coe further showed that the standard error then continued to increase with a longer postmortem interval. Most recently Adjutantis and Coutselinis [2] have attempted to improve the accuracy of predicting the postmortem interval by drawing specimens of vitreous from each eye at different postmortem intervals and plotting the slope back to a theoretical normal value of 3.4 mEq/l. They felt that this method was satisfactory only during the first 12 h after death, but enabled them to estimate the time of death within ±1.1 h.

Osmolality

Sturner et al [74] determined the osmolality of the vitreous in 45 cases and estimated the range for osmolality in all cases to be from 280–350 mOsm/kg. The osmolality was noted to increase proportionately to the concentration of ethyl alcohol present in the blood. In the cases which were negative for alcohol the normal range (including two standard deviations) was 288–323 mOsm/kg with a mean of 305.7 mOsm/kg.

Toxicology

While toxicological procedures would not normally be considered under discussion of postmortem chemistries, there is a small body of knowledge indicating the usefulness of vitreous as a medium for certain analyses when circumstances make analysis of other body fluids impossible or undesirable.

Alcohol—Four papers [8, 21, 37, 70] have been published on determination of alcohol in the vitreous humor. These indicate that the vitreous is satisfactory for alcohol determination by any of the procedures now in common use (dichromate reduction, gas chromatography, alcohol dehydrogenase). There is some discrepancy between the reports as to the ratio of blood to vitreous alcohol but Coe and Sherman [8], in the longest series published, obtained a factor of 0.89 (that is, blood alcohol equals 0.89 times vitreous alcohol). Scott et al [66] demonstrated that determination of alcohol from the vitreous after embalming gives reliable information in relation to concentrations found in the vitreous prior to the embalming procedure.

Barbiturates—Felby and Olsen [22], in a study of 19 individuals, demonstrated that barbiturates were found in vitreous humor after diffusion equilibrium in concentrations equivalent to an ultrafiltrate of the blood. Coe [7], in a study of over 20 cases of barbiturate poisoning, substantiated Felby and Olsen's work.

Other Compounds—Felby and Olsen [22] found there was diffusion of meprobamate into the vitreous similar to barbiturate. Sturner [78] has found levels of propoxyphene and pentazocine in the vitreous at levels approximately 25 percent of those found in the serum. Amphetamines were found in levels of 40–50 percent of those seen in the serum, and other drugs such as amytriptaline and digoxin have been demonstrated to diffuse into the vitreous to some extent. Coe [7] has found ethchlorvinyl in the vitreous, and in three cases of salicylate poisoning vitreous values were found to be greater than 60 percent of those seen in the serum.

Discussion

Studies of postmortem glucose, insulin, and oxygen tension in blood all demonstrate very significant differences between specimens taken from the right side of the heart and those obtained from peripheral blood vessels. As increasingly sophisticated studies on hormones, blood gases, and enzymes are carried out, it will undoubtedly become important to be able to accurately identify the source of the material to be analyzed. Blind cardiac puncture or pooled mixed blood from the heart will not be satisfactory. For several years the author has used only specimens obtained from peripheral vessels. Subclavian puncture is almost invariably productive in cadavers that will not be examined internally. A variety of peripheral vessels is available to the prosector or pathologist when an autopsy is performed. Such specimens most closely resemble the blood that is routinely obtained from the living individual, and thus are the most logical for comparison with antemortem constituents. With proper specimens for examination, coordination of the data presented for each fluid individually show how postmortem chemistries can best be utilized to elucidate a number of clinical abnormalities.

Postmortem blood glucose levels are subject to such vagaries that they make evaluation of carbohydrate metabolism difficult. However, antemortem diabetic hyperglycemia may be diagnosed from postmortem serum values when it is known that the blood examined is from a peripheral vessel, that the postmortem interval is short, that the deceased did not die from any condition that might have produced a terminal rise in glucose, and finally that the values exceed 500 mg/dl. Confidence in the significance of the serum glucose will be enhanced by the demonstration of glucose in urine and/or the demonstration of ketone bodies in blood or other body fluids [*34*].

Because of the difficulties in interpreting postmortem serum glucose levels, many investigators have thought that a diagnosis of antemortem hyperglycemia is much better accomplished through examination of cerebrospinal fluid [*20,47*] or vitreous humor [*9,10,68*]. Of these two, vitreous is the easier to obtain, and the least subject to change from terminal conditions that produce marked elevation in serum glucose levels. The author never found values over 200 mg/dl in the vitreous without a preterminal hyperglycemia from diabetes or some other legitimate cause, and diabetic acidosis was easily established by demonstrating ketone bodies in the vitreous.

Unfortunately, extensive work on blood, cerebrospinal fluid, and vitreous has demonstrated that glycolysis occurs in each of these media after death, and work of the author [*6*] reveals that glycolysis in the vitreous may be quite precipitous. As a consequence, it seems impossible at the present time to diagnose antemortem hyperglycemia with any degree of assurance, as has been pointed out by both Coe [*9,10*] and Naumann [*51*]. Hypoglycemia may be considered to be likely when some predisposing condition such as starvation, chronic alcoholism with severe fatty metamorphosis of the liver, or an islet cell tumor of the pancreas is found in conjunction with vitreous glucose values of less than 20 mg/dl in specimens obtained less than 3 h after death.

In contrast to the difficulty in evaluating carbohydrate metabolism, evidence of nitrogen retention is easily obtained from examination of any of the fluids discussed. It has been unequivocally established that postmortem serum, spinal fluid, and vitreous levels of both urea nitrogen and creatinine accurately reflect the terminal antemortem blood levels. Furthermore, great stability of these substances through the entire prehemolytic interval has been found. A number of authors [*9,10,26,33,36,38,47,58*] have discussed utilization of postmortem urea and creatinine values in evaluating the degree of renal disease, or in establishing uremia as the cause of death where no antemortem history or postmortem

examination is possible. The author [*9,10*] has used mild degrees of urea retention combined with hypernatremia as good evidence of dehydration.

In contrast to urea nitrogen, nonprotein nitrogen shows a postmortem rise, making it unsuitable for evaluation of antemortem nitrogen retention.

One of the problems, which bothered pathologists for years, was the inability to evaluate antemortem electrolyte abnormalities after death. The problem remains for potassium metabolism and blood pH. However, recent studies of the vitreous humor have demonstrated that marked abnormalities in serum sodium and chloride will be reflected in abnormal vitreous values and, furthermore, that the vitreous levels remain constant for prolonged postmortem intervals. As a consequence, Coe [*9,10*] has found it possible to demonstrate the presence of antemortem hypernatremia and hyperchloremia in cases of neglected children and incapacitated adults. Decreased levels of both sodium and chloride have been demonstrated in some infants who died with the sudden infant death syndrome [*75*], and in some alcoholic patients who died suddenly with no apparent pathology other than fatty metamorphosis of the liver [*77*] and with the presence of pyloric obstruction with prolonged vomiting [*9,10*].

While it is known that calcium remains constant in the serum during the early postmortem interval, there is no available literature to indicate that any antemortem abnormalities of calcium metabolism have been diagnosed after death. Further work is necessary to show that clinical cases of hypocalcemia and hypercalcemia are accurately reflected in postmortem specimens. However, as discussed earlier, this will not be possible with the Autoanalyzer utilizing the cresolphthaline complexone method.

With the demonstrated stability of total cholesterol and other lipid substances in the serum, attempts have been made with some success to correlate the present of heart disease with abnormalities of fatty constituents of the blood [*17,18,71*]. The stability of cholesterol also means that postmortem evaluation of the total serum cholesterol can be utilized in evaluation of liver function and in cases of questionable thyroid dysfunction.

Evaluation of liver function from postmortem studies remains limited. It has been demonstrated that in the jaundiced individual, postmortem serum bilirubin values accurately reflect the antemortem degree of jaundice. However, an apparent slight rise in postmortem values demonstrated by the author makes determination of the bilirubin unsatisfactory for the evaluation of minimal chemical jaundice in equivocal cases of liver disease. Postmortem proteins do accurately reflect antemortem values, and inversion of the A/G ratio carries the same significance after death as it would clinically before demise. However, all enzymes which would be of value in demonstrating liver disease show such erratic postmortem elevation as to be uninterpretable.

Determination of postmortem serum proteins by chemical analysis, electrophoresis, and immunoelectrophoresis reveals that they accurately reflect antemortem levels of the various fractions. Such determinations have been extensively employed by a number of investigators [*12*] to demonstrate that no hypogammaglobulinemia exists in the majority of cases of sudden infant death syndrome. The author has demonstrated true agammaglobulinemia in postmortem blood from an individual clinically known to have this condition prior to death, and has further demonstrated monoclonal elevation in the gammaglobulin of a postmortem serum from an individual who died of myeloma.

Extensive studies by many workers have shown that postmortem variations occur quite rapidly in most enzymes (acid phosphatase, alkaline phosphatase, amylase, transaminase, lactic dehydrogenase, etc). However, in contrast to the enzymes listed, both true and total blood cholinesterase remain very stable for prolonged postmortem periods. This is of

great significance to the forensic pathologist who can establish the presence of organic phosphorus poisons by the fall in cholinesterase values [*57*].

Work on postmortem levels of hormones is just beginning. The limited data available have already been used to show that cases of Waterhouse-Friderichsen syndrome may have normal cortisol values after death. The author has found a postmortem cortisol level an aid in excluding Addison's disease as a cause of death in an individual who died with hyoplastic adrenal glands. Postmortem thyroid function studies have also assisted the reviewer in evaluating a case of severe chronic thyroiditis found at autopsy [*11*]. Finally, knowledge of postmortem insulin values has enabled both Sturner [*72*] and the author to diagnose causes of insulin poisoning.

Study of blood gases after death has received little attention to date. Experimental work indicates that asphyxial deaths may be distinguished from cardiac arrhythmias by the level of oxygen tension in postmortem left ventricular blood. This needs substantiation, but Patrick [*55*] felt that the low PO_2 found in babies who died of sudden infant death syndrome was an indication that such deaths are associated with respiratory obstruction or some cessation of respiration before discontinuation of the heartbeat.

A brief comment can be made concerning vitreous humor for toxicological procedures. Coe [*8*] has found the determination of alcohol in vitreous to be excellent support of serum values, when the question has been raised as to possible contamination of blood specimens by tissue or other body fluids in cases of severe trauma. More recently, Scott et al [*66*] have demonstrated that vitreous humor can be utilized in an embalmed body for determination of alcohol when no blood is available for analysis. The results quite accurately reflect the value that would have been found in the body prior to injection of the foreign fluid. The establishment that a number of toxic substances do diffuse into the vitreous humor [*73*] will undoubtedly become valuable, as investigators run into cases where the usual blood or other body tissues are unavailable or inadvertently contaminated for the substance to be examined.

Finally, a statement should be made concerning the use of postmortem chemistries in determining the postmortem interval. Schleyer [*65*], in his excellent review article, has evaluated the chemical determinations in serum and cerebrospinal fluid, finding tests for amino nitrogen, nonprotein nitrogen, creatinine, ammonia, and inorganic phosphorus all to have some prognostic value. However, the range of error for each individual test is very large. For greatest accuracy, combinations or chemical determinations must be obtained as listed in Table 1 taken from Schleyer's review.

The present reviewer prefers the use of vitreous potassium to the tests suggested by Schleyer. As a consequence of the slow diffusion of potassium into the vitreous, there is a longer postmortem interval (during which changes in the vitreous potassium can be used as a measure of time) than is true with any of the substances so far studied in blood or cerebrospinal fluid. This is shown in Fig. 1, taken from some of the author's previous work [*6*]. While the accuracy of the procedure utilizing a single vitreous potassium is subject to great error, it would appear to be at least as reliable as any of the other chemical tests so far developed. Possibly drawing fluid from each eye at different times, as suggested by Adjutantis and Coutselinis [*2*], will increase the accuracy of the method even when the procedure is carried beyond the 12 h recommended by the authors.

TABLE 1—*Synopsis of optimal biochemical examinations of blood and cerebrospinal fluid in determining time of death (from Schleyer* [65]).

	Time since death (h)	
	Maximum	Minimum
Amino Nitrogen not exceeding 14 mg/100 ml (plasma and cisternal fluid)	10	...
Nonprotein Nitrogen not exceeding 50 mg/100 ml (plasma)	12	...
not exceeding 70–80 mg/100 ml (cisternal fluid)	24	...
Creatine not exceeding 5 mg/100 ml (plasma and cisternal fluid)	10	...
not exceeding 10 mg/100 ml (cisternal fluid)	30	...
not exceeding 11 mg/100 ml (plasma)	28	...
Ammonia not exceeding 3 mg/100 ml (plasma)	8	...
not exceeding 2 mg/100 ml (cisternal fluid)	10	...
Inorganic Phosphorus exceeding 15 mg/100 ml (plasma and cisternal fluid)	...	10

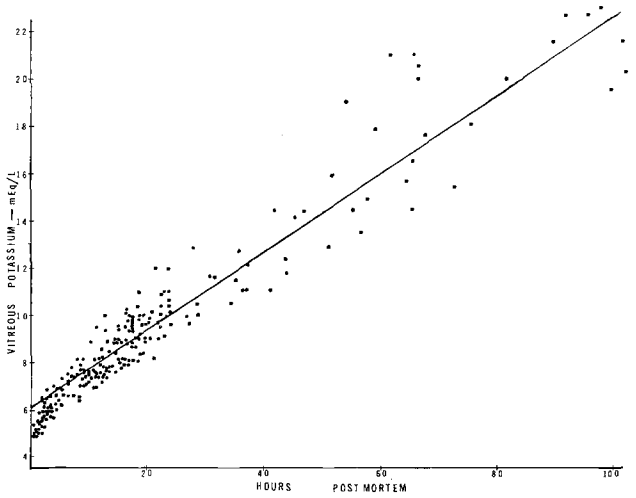

FIG. 1—*Vitreous potassium values of normal individuals plotted against the time after death with the line of least squares regression for all values having a postmortem interval of more than 6 h. The slope is 0.1625 mEq/h and the intercept is 6.19 mEq/l* (*Coe* [6]).

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