TABLE I.

Material Injected	No. of Animals used	Animals showing glomerular hemorrhages at autopsy	Animals showing no hemorrhages at autopsy	Animals showing glomerular hemorrhages
				%
Living *Strep. viridans*	29	9	20	45
Heat killed *Strep. viridans*	23	4	19	21
Berkefeld filtrate of broth culture *Strep. viridans*	79	17	62	28
Broth alone	90	0	90	0

age in the rabbit. As far as we are aware, this is the first time that a condition comparable to acute hemorrhagic glomerulo-nephritis has been produced experimentally by means of a bacterial filtrate.

Whether or not we are dealing with a true toxin cannot yet be stated. We have evidence, however, that the renal damage in our experiments has nothing to do with allergy. We can offer no explanation for the differences in individual susceptibility to the injurious substance in these experiments. The same problem confronts us in cases of infection with the *Streptococcus viridans* in the human being. Our efforts to concentrate the toxic principle of the filtrate and so to obtain, possibly, a higher percentage of instances of renal involvement have not yet been successful. Our experiments planned to subject animals to repeated injections over a period of time are incomplete. In a limited number of experiments in which filtrates of cultures of other bacteria were injected, no renal changes were produced.

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Induction of Anesthesia in Man by Intravenous Injection of Sodium Iso-Amyl-Ethyl Barbiturate.

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During the last 6 years the sodium salt of iso-amyl-ethyl barbituric acid has been used extensively as a general anesthetic in

animal experiments.[1] The difficulty experienced in preparing strictly uniform solutions of this substance and the tendency of such solutions to deteriorate on standing have heretofore prevented the utilization of this preparation for the induction of general anesthesia in man.

Sodium iso-amyl-ethyl barbiturate may, however, be prepared in a pure, anhydrous form, and if sealed in a glass vessel for protection against moisture and carbon dioxide is perfectly stable even when subjected to severe durability tests. The variations in anesthetic value previously noted appear to have been due in part to impurities, in part to slight variations in the pH value and in part to hydrolysis and decarboxylation on standing in solution.

Highly purified preparations of the sodium salt adjusted so that their 10% solutions in pure distilled water show pH values between 9.5 and 9.8 by the electrometric method, using the Bailey hydrogen electrode, give a maximum anesthetic effect with a minimum degree of toxicity when injected slowly by the intravenous route in dogs. A lowering of the alkalinity to the point at which a 10% solution shows pH values of 9.2 to 9.3, accompanied by the development of a slight opalescence or cloudiness due to commencing separation of traces of the barbituric acid compound, causes a striking loss in anesthetic value and a marked increase in toxicity. Such solutions even when slowly injected may cause Cheyne-Stokes breathing and other toxic effects on the respiratory center.

Since the sodium salt of iso-amyl-ethyl barbituric acid is almost entirely converted into the relatively water insoluble barbituric acid at a point considerably above that at which the water phase of the blood is supposedly buffered, pH 7.3 to 7.4, it might be anticipated that the injection of the 10% solution of the salt into the blood stream might easily result in sufficient precipitation to cause respiratory and other disturbances similar to those resulting from the injection of the already opalescent or slightly precipitated solution. There is, however, no trace of any such effect provided the solution is perfect and a given rate of injection is not exceeded, but even a perfectly prepared solution, if injected too rapidly, will affect the respiratory center. These results make it appear highly probable that the affinity of the cell surfaces and other lipoidal components of the blood for the released barbituric acid molecules is such that provided a given rate of injection is not exceeded, the accumulation of the product in the water phase of the blood does not reach the point of

[1] Swanson, Edward E., and Page, Irvine H., *J. Pharm. and Exp. Ther.*, 1927, xxxi, 1.

incipient precipitation with the accompanying toxic effect on the respiratory center.

40 to 50 mgm. per kilo of this preparation injected slowly by the intravenous route in a dog causes unconsciousness in 3 or 4 minutes and sufficiently deep anesthesia for surgical operation in 20 minutes. This anesthesia lasts for a period ranging from 1 to 3 hours depending on the dose employed. Dogs, when subjected to abdominal and other operations, have not exhibited any evidence of inadequate anesthesia, and the blood pressure has remained unchanged except in those cases in which severe hemorrhage has occurred.

Following anesthesia there is a somewhat prolonged period of post-operative sleep from which the dog may usually be aroused. However, it appeared desirable, before using this preparation extensively for the induction of general anesthesia in man, to find some means of antidoting or counteracting the post-anesthetic effects. This has been accomplished in dogs by injecting intramuscularly 1 mgm. ephedrine sulphate per kilo followed by 5 mgm. caffeine sodium benzoate per kilo. Dogs which have received such injections shortly after operation, when subsequently presented with food, will sniff the food, begin to eat and exhibit other signs of consciousness, whilst control dogs which have not received such injections may fail to react to the food.

This purified preparation of Sodium iso-amyl-ethyl barbiturate has given excellent results in the induction of general anesthesia in man in about 300 cases. The surgical anesthetic dose for man appears to be considerably smaller than that for the dog and ranges from 20 to 25 mgm. per kilo. There is no definite information available regarding the lethal dose of this preparation for man, but such meagre information as may be gathered from attempts at suicide, etc., makes it appear probable that the ratio between lethal and anesthetic dose is higher for man than for the dog. However, in the absence of any definite information regarding this point extreme caution has been observed in the conduct of these experiments and the dose employed has seldom exceeded 1.25 to 1.5 gm.

A dose of 10 to 15 mgm. per kilo has generally produced adequate anesthesia for satisfactory and unembarrassed manipulations in minor surgery. This dose has also sufficed for the control of convulsions in eclampsia, strychnine poisoning, epilepsy, tetanus and rabies, for periods of 6 to 10 hours.

20 to 25 mgm. per kilo have been employed to produce complete surgical anesthesia in cases in which other general or local anesthetics were contraindicated or inconvenient to administer, *e. g.*, mastoidectomy and operations on the face. However, for surgical an-

esthesia, wherever possible, this preparation has been used in conjunction with other general or local anesthetics.

The intravenous injection of from 12 to 20 mgm. of this preparation per kilo prior to the administration of ether or nitrous oxide and oxygen, has generally made it possible to reduce the amount of the supplementary anesthetic required to 20% or 25% of the quantity usually employed.

A similar dose used in conjunction with procain infiltration of the skin has permitted of extensive surgery of the abdomen with a greater degree of anesthesia and more muscular relaxation than when procain was used alone. It has seldom been found necessary in such cases to infiltrate the muscles and deep tissues with procain. The use of this combination seemed particularly advisable in those patients which were poor anesthetic risks.

The action exerted by Sodium iso-amyl-ethyl barbiturate when injected intravenously in diminishing the toxic and convulsive effects of local anesthetics, particularly procain, as recently reported by Loevenhart, Knoefel and Herwick,[2] and by Isenberger,[3] affords a further argument for the use of this preparation in combination with local anesthetics.

In surgery of the thyroid gland the technique of inducing anesthesia in the patient's room and without his knowledge, thus eliminating psychic stimulation of operating room and personnel, appeared highly desirable.

It is of the utmost importance that the preparation should be in perfect solution before being injected and that the rate of administration intravenously should not greatly exceed 1 cc. per minute. The patient is usually carried rapidly through the stages of anesthesia, so that excitement and laryngeal spasm are rarely observed. Sleep, as a rule, commences within 3 to 5 minutes and surgical anesthesia with complete relaxation of the muscles, and loss of the common reflexes except the pharyngeal, sphincters, etc., occurs within 15 to 20 minutes after starting the injection. The respirations are those of a patient in profound sleep, more often increased than decreased in rate, somewhat diminished in amplitude but regular. The blood pressure may decrease 15 to 30 mm. during the time of injection but rapidly regains its previous level.

Surgical anesthesia lasts for a period of 1 to 3 hours dependent in some measure on the dose employed. After maximal anesthetic

[2] Knoefel, P. K., Herwick, R. P., and Loevenhart, A. S., *J. Pharm. and Exp. Therap.*, 1928, xxxiii, 265.

[3] Isenberger, Robert M., *Proc. of the Staff Meetings of the Mayo Clinic*, 1928, iii, 40, 294.

doses the patients may sleep from 3 to 10 hours and occasionally longer. Nausea, retching and vomiting have not been observed in any of the cases. Frequently patients when coming out of sleep become restless before they are fully conscious. Morphine administered in the usual amount exerts a quieting effect.

In those cases in which maximal anesthetic doses have been employed, in which it is desired that the patient should awake somewhat sooner and fully alert mentally, 25 to 50 mgm. of ephedrine sulphate injected intramuscularly, followed by 0.65 to 1 gm. sodium caffeine benzoate, one-half to 2 hours after the operation, has exerted the desired effect.

Detailed papers covering the clinical, pharmacological and biophysical-chemical aspects of the case will shortly be published.

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A Consideration of the Pyridine Test for Chloroform.

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A method for the quantitative measurement of minute amounts of chloroform has been described by Cole.[1] An attempt was made to use this test to determine the amount of chloroform in sea water, in which small marine organisms were being anesthetized. Certain difficulties were encountered, many of which arose from the fact that the accuracy of the test was not known. This led to the study of the accuracy of the test discussed below.

A series of 105 tests were made upon a given concentration of chloroform in sea water. The test consists of mixing 2 cc. of 20% NaOH in distilled water, 1 cc. of pyridine and 1 cc. of the chloroform solution in a test tube and placing the latter in a water bath at 100° C., a red or pink color appearing in the mixture at this time. Precautions are taken to eliminate errors due to evaporation. When the chloroform is in sea water a precipitate forms; this is thrown down with a hand centrifuge. When distilled water is used no precipitate is formed. The tube is then cooled to about 18° C. and placed in a comparator box so arranged that several tubes can be arranged one behind the other, the color within the tubes being summated to give an intensity of color greater than that of any one

[1] Cole, William H., *J. Biol. Chem.*, 1926, lxxi, 173.