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Cause and elimination of reactions following intravenous injections

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THE CAUSE AND ELIMINATION OF REACTIONS FOLLOWING INTRAVENOUS INJECTIONS

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The value of infusions has generally become well accepted, but their effectiveness is often marred by untoward reactions which frequently occur at the most inopportune times. There is a legitimate and growing field for intravenous treatment, and the indications and contraindications for it are becoming more sharply defined. This form of treatment is considered so important that in the Mayo Clinic it is handled by a special committee appointed to consider matters such as the advisibility of its use, the choice of materials, the purity of drugs, the adequate daily supply of distilled water, and the methods of preparation and administration.

Reactions, as we know them, embody a variable degree of damage to the body physiology. Typical pyrogenic reaction consists of a rigor and a feeling of chill from fifteen minutes to eight hours following injection. There is a sharp rise in temperature and pulse rate followed by profuse sweating and a fall in temperature. There may also be cyanosis, diarrhea, nausea and vomiting, headache, albuminuria, collapse, and death. Even the mildest reactions are uncomfortable, and severe reactions are always dangerous, especially so in the case of a serious illness. Physicians and surgeons agree that

reactions present a highly undesirable toxic side action of intravenous therapy, and owing to the fact that a considerable proportion of patients who receive infusions are in a dangerous condition, it is not possible to estimate to what extent reactions may be an actual cause of death. These are the risks that are inherent in the introduction of any foreign substance into the blood stream in which the integrity of a multiplicity of chemical, physiological, and physiochemical balances must be maintained as essential to life.

It has long been known that injections of fluids into a vein or under the skin of man may cause a fever. As early as 1865, Billroth reported reactions in dogs. Later, the numerous salt fevers and salvarsan fevers were thought to be specific types until Wechselmann pointed out that if salvarsan solution was carefully prepared with freshly distilled water, no reaction occurred.(1) At that time, he postulated that the reaction was not due to the salvarsan but to contamination products of the solution. In 1909 and 1910, German papers assumed that the reaction was due solely to the salt injected and not to the water in which it was dissolved. They further stated that the fever is proportionate in extent to the amount of salt injected. However, in 1911, Hort and Penfold (2) found that distilled water would give the same reaction. They then studied Wechselmann's paper which called attention to the fact that the water was not sterile and admitted that nineteen per cent of the cases still showed reaction of fever even after the water was filtered and heated. Experiments by Hort and Penfold proved the ineffectiveness of filtration and centrifugation in removing the fever producing properties of any sample of water which

had been allowed to stand. Freshly distilled water, however, did not give reactions. They were the first to suggest that the fever produced by injections of water which had been allowed to stand was caused by soluble products, perhaps of bacterial origin, and was not due directly to the bacteria as such or to the unaltered protein. In a further report in 1912, they definitely justified the non-existence of "salt fever," "ferment fever," "sugar fever," etc. Several factors remained undecided; what the fever producing substance was, where it came from, and how it developed. They called it a pyrogenic substance and suggested that it was of bacterial origin.

The cause of febrile reactions following intravenous or subcutaneous fluids has been sought assiduously, and every possible agent has been suspected. In this paper I shall attempt to present those factors which have been most generally considered.

Many writers have emphasized the importance of slow introduction of solutions into veins, especially if they are hypertonic solutions. Among the first to discover this were Palmer, Turner, and Gibb.(4) It has since been substantiated by Levvy,(5) Titus and Dodds,

(6) Hondon, (7) Hirschfeld, Hyman, and Wanger, (3) and Hyman and Hirschfeld.(9) They all call attention to the need of introducing such solutions with great deliberation, and while they do not altogether agree on the absolute speed which is recommended, and which appears to differ somewhat with different solutions, the trend seems to be toward advising a speed not to exceed three to five cc. per minute. Hyman and Hirschfeld (9) affirm this with a startling report-- almost anything can be introduced into the veins of a patient if it is done slowly enough. They manifest that even antigen may be injected intravenously into a sensitized animal without production of anaphalactic shock. On the other hand, Florence Seibert (1) has shown that the rate of injection may be left entirely to the discretion of the clinition. She took samples of pyrogenic water and injected them into rabbits--the total injection being completed in some cases in ten to twelve seonds and in others in eighty to one hundred and ten seconds. Both techniques induced fever in the same length of time after injection and to the same extent. Furthermore, she took a pyrogen free sample of water, repeated the same experiment many times, and found that there was never a

reaction regardless of the rate in injection of the fluid. During a three and one half month period from September 15, 1935 to January 1, 1936, Nelson experimented in the hospital division of the Medical College of Virginia where six hundred and eight venoclysis were given. The rate of flow varied from two hundred and fifty cc. to three thousand cc. per hour. Tremendous amounts of fluid given under the same conditions produced no chill, yet the following day under the same conditions and with the same type of fluid, a small amount given slowly would cause an intense reaction. These experiments have been confirmed by Rademaker,(11) Fantus, Seed, and Schirmer,(12) Banks,(13) Walter,(14) and others.

A few authors have brought forth the theory that the temperature of the solution has a great deal to do with the causation of febrile reactions. Little(15) states that hot fluids are a very common cause, since they alter blood and tissue with the liberation of fibrin. He further indicates that cold fluids are safe to use. This being true, in addition to the fact that the delicate thermometers used failed to register accurately, he felt more secure in insisting that the

flask fluid be at or slightly below body temperature--preferably ninety-eight degrees. Rademaker,(11) Banks,(13) Walter,(14) and Seibert (16) have, among others, definitely ruled out this factor. Walter, at Peter Bent Brigham Hospital, administered one thousand cc. quantities of ten per cent dextrose solution to patients at temperatures ranging from twenty to forty degrees centigrade with no untoward reactions. Nelson (10) demonstrated that solution temperatures varying from eighty-five to one hundred and twenty-two degrees Farenheit had no effect on his patients.

The question of the quantity of the fluid administered at one time has been suggested by a few with no substantiations. Nelson (10) and Banks (13) gave tremendous quantities of the different solutions ranging from two hundred and fifty cc. to and above three thousand cc. and eliminated this theory as being a cause of fever.

Walter,(15) Banks,(13) Nelson,(10) and others have established proof that the concentration of the solution, whether it be dextrose or saline solution, has no bearing on the production of febrile reactions. Concentration of dextrose in physiological quantities, ranging

from two to twenty-five per cent, and solutions of dextrose in isotonic saline solution from six to fifty per cent were administered to patients with no unfavorable reactions.

It has been postulated that insoluble material in the intravenous solutions may be the cause of pyrogenic reactions. The Committee on Maintenance(17) stresses careful elimination of all foreign material such as shreds of filter paper, cotton fibers, etc. in the solutions. Kyes and Strauser(18) have evidence that insoluble material of any kind when injected into the blood stream will cause fibrin deposits which are followed by a chill and rise in temperature. This factor has been eliminated by proper filtration of all solutions. However, reactions are still occurring following this precaution.

Does the hydrogen ion concentration influence the results of intravenous therapy? That this factor may be influential in the production of fever was emphasized by Williams and Swett.(19) They affirmed that if saline and glucose solutions more acid than pH 6.5 are injected into the circulation at a rate or in an amount that the blood cannot neutralize or buffer, reactions character-

ized by chills or prostration follow; whereas, if the pH was brought to that of the blood, no reaction occurred. They further concluded that stored, distilled water becomes highly acid, and that if it is used as a solvent in the preparation of intravenous fluids, it may produce a solution with a much higher hydrogen ion concentration than that of the body. Glucose solution when boiled or autoclaved becomes highly acid, and stock glucose solutions used clinically are also highly acid. The solutions may be easily corrected as to pH by the addition of buffer salts. These men specifically state that buffering of glucose and physiological sodium chloride solutions prevent reactions. Mellon, Slagle, and Acree(20) in an article, "The Practical Application of Buffers," relate that patients transfused with stock solutions of a pH 10.5 had a severe reaction. Later experiments in which neutralized solutions were used brought forth no reactions. It was obvious, they believed, that free alkali was present in the sample of a product marketed especially for transfusion work. They concluded that all solutions used intravenously should be buffered properly before introduction in order to approach very nearly blood pH. Darrow(21) has re-

ported that solutions of an alkaline pH reacted more frequently than those of an acid pH, while Falk(22) found that alkaline solutions buffered to a low pH still gave reactions. This evidence leads one to believe it was not the pH alone that caused the reaction, since alkaline impurities may have been responsible in some degree. However, by demonstrating that non-pyrogenic water with a pH range of 4.6 to 8.5 did not cause reactions, Seibert(16) carefully ruled out this factor. On the other hand, reaction producing waters did cause a fever in any range of pH regardless of conditions.

According to Seibert,(16) the German, Freund, in 1911, first suggested that hemolysis of the blood might be the cause of fever. His theory has had many followers. One of them, Yamakami,(23) brought forth what he considers to be good evidence of the existence of hemolytic fever. He arrived at the conclusion that intravenous injections of suitable quantities of distilled water give a typical fever, which he was satisfied as being due to hemolysis. In answer to this, Penfold and Robertson,(24) after repeating his experiment with elaborate care in preparation of the solutions to insure sterility and non-contamination, ascertained that no

fever resulted even when hemolysis is well marked. In addition, they state there is no reliable evidence of simple, pure hemolytic fever-- the fever of paroxysmal hemoglobinuria being due to an unkown cause. Seibert, (1) using great care and deliberation, also undertook an experiment on this phase of the problem, and her results are evidence in opposition to hemolysis as a cause of fever. Therefore, hemolysis may be discounted as a factor.

In order to present a complete analysis of the situation, one must consider to what extent hypersensitiveness or immunity of the individual may enter into the results. According to experiments conducted by Seibert,(1) it has been proved that the resistance of a particular animal is not the determining factor in fever production, but rather that the reactions are dependent upon the nature of the agent injected. It was also demonstrated that there was no indication of an immunizing or sensitizing effect, i.e., the reaction symptoms depended on the water injected rather than upon the number of previous injections.

A few authors, including Kyes and Strauser,(13) feel that the patient's condition at the time of veno-

clysis may materially effect the results. As an index to this probability, they suggest the shortening of the clotting time of the patient through the prolonged use of a tourniquet which increases the fibrin content of the blood in that part of the body affected. Nelson's (10) use of hypodermoclysis with production of the same untoward results contraindicates this as a cause for reactions.

Specific ion effect was believed by some to be the cause of febrile reactions following intravenous therapy. The findings of Hort and Penfold give evidence to the fact that sodium chloride solution up to twenty-five per cent concentration did not produce fever when made with freshly distilled water. Seibert, also, has grounds for rejecting the specific ion effect. Sodium chloride solutions in concentrations of 0.9%, 8%, and 10% caused no fever. Nor did solutions of amonium chloride, amonium sulphate, sodium hydroxide, sodium bicarbonate, and hydrochloric acid, provided they were in concentrations used as solvents and made up in freshly distilled water. Moreover, a buffer solution containing sodium, potassium, calcium, magnesium chloride, and phosphates in a pH about 6.8 gave no febrile re-

actions. To further dispense with this theory, Seibert illustrated that, without a doubt, a pyrogenic substance is not of a character or present in sufficient quantities to be visible in a spectrum. Evidence for this theory was found in a negative spectroscopic study of a positive reaction producing water.

Laboratory gases; carbon dioxide, oxygen, hydrogen sulphide, and nitric acid fumes were suspected at one time to be the cause of the development of pyrogenic properties of water. These were studied by Seibert, but no direct evidence was found for attributing fever producing properties to them.

By injecting water which had been standing in a soft glass bottle for years, Seibert ruled out the theory that glass dissolved in water could be a cause for reaction. Furthermore, glass wool was placed in freshly distilled water, and although some of the glass went into solution as seen by the increase in pH, no reaction occurred.

Nelson,(10) Rademaker,(11) Fantus et all,(12) and Walter(31) ahve eliminated the rubber tubing as a direct cause of pyrogenic reaction, since they adhere to the

belief that protein residues in rubber tubing and needles may contain some pyrogenic substance which is "leeched out" during the transfusion, and which may be completely eliminated if these parts of the apparatus are thoroughly cleansed prior to use.

Is a filterable substance the cause of fever? The conclusion that water produced fever whether it was filtered or not was arrived at by Seibert.(1) She demonstrated that although fever producing water was filtered through a clean Berkefeld candle, there was no alteration in the reaction produced by the solution when injected. In other words, the fever producing substance is filterable.

Still to be considered is the water used in the preparation of the solutions. All waters do not cause a fever following injection, but it seems to be an unquestionable fact that tap water drawn at certain seasons of the year; namely, January, February, June, and November, always produced a fever. Distilled waters taken from diverse tanks showed a variability in this respect. In studying the bacteriology of the waters, Seibert(1) discovered that if water is kept sterile following proper distillation and preparation, it will not

water simulates the creation of an organism. However, if this substance is of bacterial origin, it is certainly not identical with the bacterial bodies since it is not eliminated by filtration through a Berkefeld filter. Because immediate autoclaving prevents reactions, it follows that growth of some type must be occurring in and contaminating the solution. Thus far the evidence presented has not eliminated the presence of a filterable virus, but Seibert(1) has ruled out this possibility by innoculation of sterile pyrogen free water with a fever producing Berkefeld filtrate, which procedure did not lead to the development of a pyrogenic solution.

The question naturally arises as to whether the substance is a bacterial-toxin. If this were true, the substance would be expected to be heat-labile--a fact which was confirmed. Since the degree of reaction depends on the length of time heat is applied to the solution, and since the toxic substance can be completely destroyed by refluxing for seven hours, the toxic substance in the pyrogenic water may be completely destroyed by long, drastic heating.

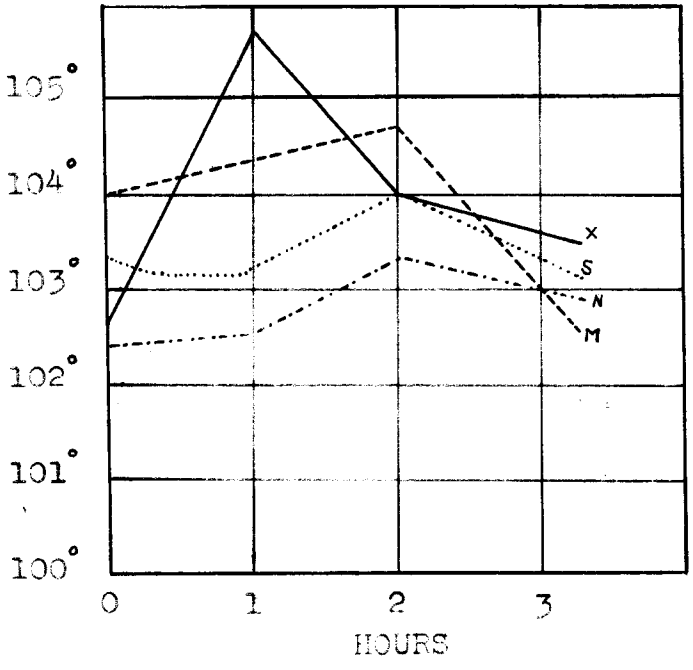
All evidence so far indicates that the pyrogen in distilled water is a filterable, heat-labile, non-voli-

tale, fever producing product, probably of bacterial origin. It has been shown by Nelson,(10) Seibert,(1) and others that non-pyrogenic water if innoculated with undistilled pyrogenic water will become reaction positive after standing several days. Since immediate autoclaving will prevent this development, it follows that growth of some type, which is an essential factor in the development of toxicity, must be occurring in and contaminating the solution. Nelson,(10) in addition, brought forth conclusive evidence which reduced the percentage of chills very abruptly by changing only one factor in the preparation of solutions. Improper distillation together with possible contamination after distillation may reasonably be inferred to have caused the majority of chills. Consequently, a new still was installed. In an effort to determine the time of contamination, a series of one hundred and twenty hypodermoclysis were run. Hypodermoclysis was chosen for these reasons; the type of reactions was familiar, and they were more constant than those following venoclysis. Two different physiological saline solutions were used; the first was the solution ordinarily sent to the operating room, and the second, a special pre-

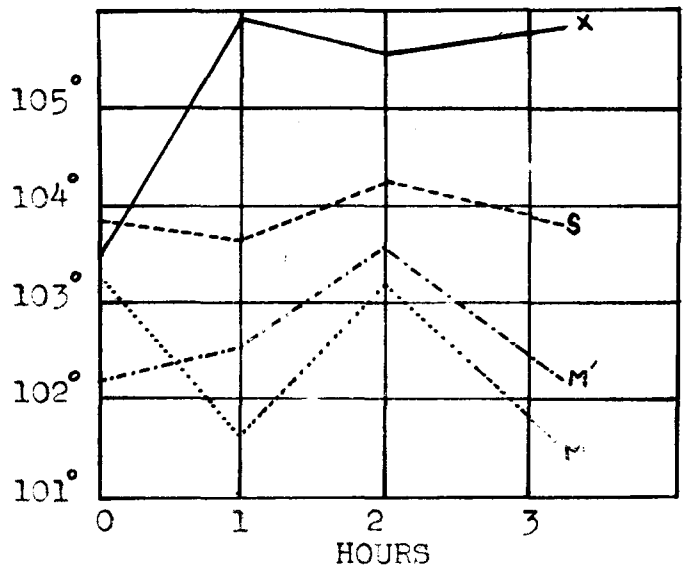
paration, was the water taken directly from the still, filtered, and immediately autoclaved. In this experiment, seven hundred and fifty cc. of each solution, the special and the ordinary, was given in the lateral aspect of the thigh, using apparatus selected at random from the hospital supply. Within twenty-four hours, the thighs were compared both objectively and subjectively. It was a startling fact that in ninety-three per cent of the cases the thigh receiving the ordinary solution showed local signs of inflammation with swelling, redness, tenderness, and heat; whereas, on the other leg no such phenoma was evident. Accordingly, cultures were taken from the bottle of water which was standing in the operating room, and the following organisms were found; Escherichia Coli, Escherichia Communior, Bacillus Alcaligines Faecales, Monilla Albanicans. Algae had previously been ruled out by the fact that water taken from the still was non-reactive while that from the storage tank was reactive. Sunlight, which is necessary to the growth of algae, could not reach the water in the tanks. Having the impression that these and possibly other bacteria or their growth products were the cause of chills, experimenters felt that it

should be possible to produce pyrogen by innoculation of waters with pure cultures of various bacteria, and so detect whether or not one or more than one type was responsible. This was done by Seibert(16) and substantiated by Nelson(10), and it was found that not all bacteria produced pyrogen, but rather that it is a product of specific strains of bacteria. An example of their thorough work is demonstrated by this experiment in which the following technique was used: one hundred cc. flasks, after being carefully washed and rinsed with freshly distilled water, were then partially filled with water taken directly from the still and autoclaved immediately. These flasks were seeded with the organism by removing a loopful of the growth from the agor slant and washing it into the flask. The flasks were recapped and allowed to stand for various periods of time, ranging from one to seven days, after which they were again autoclaved and filtered. Not all the flasks were seeded---some being retained as controls. Before each solution was tested, sufficient sodium chloride was added to a ten cc. quantity of the water to make it a physiological solution. These samples were injected into the ear veins of a rabbit, separate

syringes and needles being used in each case. The temperature of the rabbits were taken at one hour intervals, and graphs were made. Immediately following are reproductions of two illustrative graphs from Nelson's work.



Thirty-six hour cultures. X- B. Alcaligenes Faecalis; M- Monillia Albicans; S- Physio. solution of NaCl; N- No Injection.



Seven day cultures in which growth was profuse. X-Bacillus Alcaligenes Faecalis; M and M'-Monillia Albicans; S-Physiological NaCL Solution (control).

From these reproductions, one can see that intravenous administration of B. Alcaligenes Faecalis solution always produced a fever, and that both Monillia Albicans and normal saline solutions never produced a typical febrile result. Nelson(10) repeated this experiment in humans and was able to illustrate that the same contaminated water causes chills and fever; whereupon, Hort and Penfold(25), in their paper, suggested Bacillus Typhosis as a reactor. Banks, (13) following a complete study using rabbits, found that all factors were excluded except the bacteriologic one and added the Pseudo-

monas Scissa and Pseudomonas Grene to the growing list of pyrogen producing bacteria. And Seibert(16) added many other organisms to both divisions; namely, the reactors and the non-reactors. She divided them into four groups, the last of which might be the cause of terrific reactions that occasionally follow venoclysis, and which may be referred to as "speed shock". In using common bacteriological tests in regard to the cultural growths, she found that all the positive reacting bacteria were slow growers and could be grouped as chromogenic and non-chromogenic organisms. These specific bacteria all survived in distilled water, some for many months, presumably upon the gases absorbed from the air or upon their autolized predecessors. Quoting from Prescott and Winslow in their Elements of Water Bacteriology (1915), she says, "They, therefore, seem to fall into the protrophic bacteria." Banks(13) also differentiated between the types of bacteria and their reactions by comparing pyrogenic water procured from chromobacteria growths with pathogenic(staph aures) and non-pathogenic(B. Subtilis) organisms. He demonstrated that the fever produced following introduction of the pyrogenic water was typical in that it was immediate,

and the fever usually returned to normal within two hours; while the pathogenic and non-pathogenic water, as he used them, produced a much delayed temperature response usually extending to several hours. The recovery in these latter cases was more gradual and prolonged over a period of several hours; whereas, the pyrogenic water treated animals were alert and active in two hours. Therefore, it seems the specific property of the chromobacterium is that of fever production. Since B. Alcaligenes Faecalis produces almost identical temperature graphs, such as those shown in Bank's paper, there would seem to be no necessity to limit these reactions to the activity of one group of organisms. Nelson,(10) also, demonstrates that this organism will cause chills in human beings.

What, then, is the nature of this pyrogen? By a process of elimination, it has been proved by many investigators to be a soluble, filterable product of bacterial origin. It is not essential for the pyrogen to be in the form of intact bacteria since Berkefeld filtrates of potent water elicit fever as well as unfiltered water. For this reason, pyrogen must be a chemical substance in solution, or a colloidal aggregate of

a size which will penetrate the pores of a porcelain candle. As noted before, it is not living substance of the nature of a virus; neither is it a bacteria which is of undetectable size, since innoculations of non-fever producing waters with potent filtered waters did not lead to the development of the feared symptom complex following injection. It may be destroyed by heat, but this is a long, tedious process and for practical purposes it is of no concern. Boiling for six or seven hours will produce non-reactive water, and autoclaving, if sufficiently prolonged(from three to four hours) will also destroy the factor. However, the usual period of sterilization, according to Nelson(10) will increase the activity of the solution. The substance is soluble in water, and if a non-pyrogenic water is placed in a flask which, although now dry and sterile, had formerly contained some reactive water that was not thoroughly washed out, the water will dissolve sufficient pyrogenic substance from the sides of the flask to become potent. Perhaps this is the reason that tubing and venoclysis apparatus may occasionally be the cause of reactions, the dry pyrogenic substance being picked up as the solu-

tion passes through the set. McClosky, Schrift, and Yates(26) say the agent is of a particulate nature with a longer order of magnitude than fifty millimicrons but smaller than one micron. They find that the substance can be eliminated from the water by special filtration methods; i.e., with a two hundred second Zsigmondy filter. Nevertheless, it will pass through a forty-two second filter. Seibert(16) attempted to study the pyrogen further by chemical analysis. Concentration was necessary, and this was done by slow distillation of small amounts of reactive water using diminished temperature and pressure. By this method, she was able to concentrate the substance to some degree and upon testing its reactive power, discovered that the height and length of the fever curve was somewhat proportional to the amount of material injected. For instance, with smaller amounts the curve flattened out, making it easy to determine the minimum amount of substance which would produce a reaction. After the solution elicited a maximum temperature rise, larger, more concentrated doses merely increased the duration of the rise rather than the height of the curve. Finding that she was able to concentrate the active agent to a con-

siderable degree, her next step was an attempt at qualitative analysis. With considerable proof that the reactable substance was of bacterial origin, the question arose as to whether the pyrogen was a protein or at least a nitrogenous substance. A micro-nitrogen method of analysis was devised, and by repetition it was found that fever producing water contained slightly more nitrogen than non-reacting water. By calculation the amount of nitrogen demonstrated by analysis was equal to five hundred millionths gram of protein per cc. of solution. This, of course, was much too delicate a test for the Ninhydrine reaction, and for this reason, it cannot be definitely stated at the present time that the pyrogen is not a protein. More delicate tests can be devised before this can be proved. Rademaker(11) also arrived at the same conclusion as Seibert, but he found a greater amount of combined nitrogen and organic matter in pyrogenic water. By distilling pyrogenic water in a vacuum at three hundred and fifty degrees centigrade and using no trap in the still, the first fraction was very toxic. Potassium permanganate solution splits the unknown substance by digestion at one hundred

and five degrees centigrade, and a precipitate of a brownish, gelatinous, visible material occurs with amonia being driven out.

This pyrogenic substance, although not completely isolated and analyzed, does contain nitrogen. From a more practical standpoint, Carter,(27) in searching for some test to measure the presence of a pyrogen in distilled water, suggested that since there must be oxidizable material in the solution, the U.S.P. test for such substances could be used. This test,(U.S.P.X) directs heating to boiling one hundred cc. of distilled water, acidulating with ten cc. of diluted sulphuric acid and treating with one-tenth cc. of tenth normal potassium permanganate solution. The color of the solution produced by the permanganate should not disappear for ten minutes following boiling, providing there is no oxidizable material present. He indicated that this test could be adapted to measure pyrogen in water intended for venoclysis. Many tests were made, and he found that fresh, properly distilled water will pass a much more delicate test. The method which he proposed seems to intimate that distilled water which does not dis-

charge the color is pyrogen free. In preparing the solution, he used the same quantities as directed by U.S.P., but reduced the amount of potassium permanganate to one half by using a one twentieth normal solution. To further confirm the relation of pyrogen to bacteria, he demonstrated that water which did not respond to the test would quickly discharge the color if allowed to remain in a warm room over night. Banks(13) renders the conclusions of Carter questionable by suggesting that the proposed test is totally inadequate. He showed that if the original sensitivity was multiplied one hundred times, it could fail to indicate the presence of a pyrogenic substance.

Although it is not yet widely enough realized, the cause of pyrexial reactions following intravenous injections has been definitely established, and many of the traditional factors have been proved to be of relatively little importance. It appears that there are but two fundamental requisites for a safe supply of water suitable for venoclysis; namely, an unlimited source of freshly distilled water and some type of centralized responsibility for the preparation of these solutions.

The production of a fresh, pyrogen free water entails but one outstanding factor--an adequately equipped and correctly operated distilling apparatus. Nelson(10) reduced the percentage of chills from twenty-eight to one and four tenths during which time the only factor under consideration which changed was the introduction of a new still. Rademaker(28) had almost identical results when he changed the still in use. He had the Barnstead Still and Sterilizer Company design a suitable distilling apparatus which was of the continuous distilling type with a horizontal condenser. Multiple baffle plates were placed in the upper portion of the still and a smaller set in a vertical position within three inches of the pipe condenser. This system forces the steam to turn many angles, striking against numerous plates, and thus losing the spray. In addition to this, the Seveninghaus deconcentrater was attached. It consisted of a one fourth inch brass pipe introduced through the bottom of the still and attached to the waste pipe and air vent by a valve. The tube rises in a vertical position in the center of the reservoir about one third of its height. The level of the water is kept approximately

one half inch above the open end of the tube, and when the valve is open, the surface of the water is constantly in motion toward its center, and it is this motion which greatly diminishes the formation of spray. The increased concentration at the surface, another cause of spray formation, is also prevented by this tube. Rademaker(11) stresses the importance of keeping the still very clean and set up the following rules: 1.Distill slowly, (prevents excess foaming) 2. Distill for fifteen minutes into waste, (this cleans out accumulated products) 3. Deconcentrate with sufficient rapidity, 4. Clean the entire apparatus every six months, removing the boiler scale and nitrogenous products. He is convinced that failure to observe any or all of these percautions will lead to poor results. Perkins(29) uses the vertical type still, rather than the horizontal, which is also equipped with a double set of baffle plates. His objection to the horizontal type is an air pocket from which the distillate may absorb diliterous matter. These men are sure that there are many satisfactory distilling sets on the market, especially double and triple outfits with baffle plate systems, which

are acceptable but much more expensive. The authors, Lewisohn and Rosenthal(30) insist that triple distilled water is indispensable in preventing the occurrence of chills. Most experts feel that single distillation is adequate. Among these we find Walter(31) and Rademaker. (11) Elser and Stillman(32) perceive that single distilled water can be used with safety in preparation of intravenous solutions if the necessary percautions are taken; they conclude that triply distilled water is "truly a fetish" in that it is "a material object regarded with awe, as having mysterious powers residing in it.....and from which supernatural aid is to be expected." Only a few deny that tap water contains much pyrogenic substance. Bleyer and Rohde,(33) using chlorinated city water from the river, found that the quality of the raw water was unsuitable, and even when triply distilled, the routine distillation did not destroy the substance which produced hyperexia. They had a specific problem, and on experimentation, they found that pyrogen could be broken down by high pressure steam at 60# pressure in the main. A unique mechanical device by which condensed high pressure steam could be employ-

ed for distillation instead of the city water was conceived by them. Briefly described, the method is one in which high pressure steam may be freed of impurities in the boiler system by means of continuous vacuum seal drainage and glass wool filtration. Once in operation, this method is inexpensive and can be recommended to hospitals which otherwise depend on pyrogen bearing raw water. All these men agree that should a still become contaminated due to dismantling for repairs etc., it should be allowed to run for two hours in order to procure complete freedom of contamination.

We may agree now that singly distilled water from a still adequately equipped with baffles and traps or with a reflexing condenser is safe. We must, however, have some way to keep the water sterile and therefore pyrogen free. This may be done safely by immediate autoclaving and storage. Nelson(10) says that no organism will ever be the offender if distilled water is taken from the still and immediately autoclaved. He is sure that all storage tanks are contaminated by a back flow of air when the still cools; therefore, it would seem that storage tanks are unsafe. When they insti-

tuted in the Massachusetts General Hospital a careful regime autoclaving the solution for fifteen or twenty minutes within two or three hours after it was made up, Stoddard(34) avoided reactions completely. Rademaker (11) also found that the storage of distilled water was a great problem. He kept the water in a sterile tank in which he could demonstrate no gross bacterial growth; but in one week, the water contained a pyrogenic substance. On examining the tank, the walls were covered by a nitrogen contaminated material. Repeated cleansing failed to keep the tank clean. In attempting to use a five gallon glass tank, the same difficulty was encountered. He then started a routine in which the distillate was collected in sterile glass graduates and immediately made up into the required solution. Delay of four to eight hours in sterilization was found to generate enough pyrogenic material to produce a reaction. In this case, the source of contamination and point of trouble was located by Carter's permanganate test.

Walter(31) found that the sealing of solutions after being made up was a problem, especially if they

were to be autoclaved. He used a clean rubber bushing which fitted perfectly into the mouth of a flask containing the solution. The skirt of the bushing was turned down and a channeled stem stopper of steel was inserted partially into it. The channel in this stem provides for the escape of air and steam during sterilization. The solutions are then put in an autoclave and heated at two hundred and fifty degrees Farenheit for fifteen after which the steam is shut off and the autoclave permitted to cool to two hundred degrees Farenheit before opening. In this way any concentration of the solution caused by an outburst of steam which follows the sudden reduction of pressure is avoided. As the flasks are removed, the steel stoppers are pushed in to complete the seal. During cooling a partial vacuum is formed inside the flasks, and this causes the metallic click when the flask is jarred--thus providing an easy check on the sterility of the solution. Walter finds that a solution prepared in this way may be stored indefinitely. A process of sealing the solutions with gauze, cotton, and wax which enabled them to be kept up to thirty days after sterilization was used by

Nelson.(10)

The careful cleansing of the glass, rubber tubing, and other apparatus which comes in contact with any intravenous solution is a major problem. Rademaker(28) has set up very strict rules for the washing of glassware. He stipulates first washing the glass thoroughly with tincture of green soap and hot water followed by a rinsing with tap water. Next in sequence is the submergance of the glass in potassium bichromate-sulphuric acid cleaning solution, after which it is rinsed with tap water four times and followed with six rinses in fresh distilled water. If kept sterile and used inside of two hours, this procedure meets requirements. In cleansing rubber tubing which has been demonstrated to cause reactions when pyrogenic material was absorbed from collection in the tubing, he uses the Stokes technique, i.e., the tubes are filled with ten percent sodium hydroxide for twelve to twenty-four hours--then washed in running water for two hours and boiled in distilled water for one-half hour. Walter(31) has a very similar technique in cleansing tubing and glassware. He further suggests a method to remove the "bloom"

from new rubber tubing, i.e., by treating with five percent sodium carbonate solution in an autoclave at two hundred and fifty degrees Farenheit for thirty minutes. The rubber is then rinsed with one percent hydrochloric acid followed by distilled water. Needles should be cleaned by washing in hot, soapy water and rinsing in distilled water. After this preparation, the parts are dried on a clean, dust-free sheet with the aid of suction and then assembled. Needles are placed in a sterile tube plugged with cotton. This equipment should be arranged in a clean pan, wrapped with a double thickness of muslin, and autoclaved at two hundred and fifty degrees Farenheit for fifteen minutes. They are then considered safe for ten days. Banks(13) makes the procedure considerably more simple. He feels that since pyrogen is water soluble, flasks and other apparatus may be freed of offending substance by frequent washing with pyrogen free water.

It appears that in order to prevent reactions from infusions, the proper approach to sterilization, preparation of materials, solutions, etc., almost requires a special department in hospitals. Falk(35) suggests

that a separate room be designated for this purpose, the management of which shall be placed in competent and reliable hands whose sole duty shall be the care of materials used for venoclysis. Rotation of student nurses through this department had not met with great success, due to a certain laxity which can only be corrected by a full-time, responsible person. Fantus, Seed, and Schirmer(12) inaugurated the Sterile Supplies Department in the Cook County Hospital where tubing and all other apparatus was scrupulously cleaned following use. Some authors insist that since this is such an expensive procedure, commercial houses should cooperate and furnish proper solutions in vacuum sealed hard glass containers which could be distributed to hospitals. Falk (35) believes that the expense of maintaining a special infusion room and unit in a hospital would more than cover the cost of buying a commercial product, and Hunt (36) maintains that ordinary commercial preparations and distilled water should never be used if it is possible to avoid them. He has proved some samples of glucose solutions, supposedly chemically pure, to be unfit for use. If it is necessary to use commercial prepara-

tions, one should use only those which are of established purity. From an economical standpoint, Walter(15) studied the advantages of hospital preparations over those of commercial solutions and found that if there is a use for very large quantities, it is cheaper to prepare one's own solutions. His results showed a saving of from eighty-one to eighty-seven percent over comparable commercial products.

Although the cause of pyrogen reaction is known, it is a very elaborate and somewhat expensive procedure to eliminate. What should the general practitioner or small hospital who do not have all the facilities and yet have need for large quantities of fluids which are not accessable from commercial houses do? In a much neglected paper written by Lees and Levvy(37) and published in the British Medical Journal, the solution to their problem is apparent. These men found it possible to remove pyrogens from large quantities of water by forcing it under pressure through a bed of powdered charcoal; thus making use of the so-called automatic pyrogen removing filter. From further experimentation, it develops that strongly pyrogenic water or solutions

may be absolutely freed from the reactive agent by the simple procedure of shaking for a few minutes with a very small quantity of one-tenth percent of powdered charcoal. This quantity of charcoal can readily be removed by allowing the liquid to stand for a minute or two and then decanting through a fluted filter paper into a clean, sterile receiving vessel which has been rinsed out with a little of the filtrate before collecting the remainder. This method is of great importance and very inexpensive. In present times of civil and military crisis, an emergency could arise which demanded very large quantities of intravenous solutions. If properly carried out, the above procedure is said to remove quickly all pyrogenic material from tap water or any unsatisfactory distilled water. Even though only the most primitive laboratory facilities are available, it is within the reach of everyone.

In summary one may conclude that: certain factors thought to be influential in producing a reaction following venoclysis are eliminated, and that the fever producing material, designated as a pyrogen, is a product of specific bacteria which contaminates the water.

Chemically, it is a water soluble, heat-labile, concentratable, nitrogenous substance oxidized by potassium permanganate, of a particulate nature, and filterable through a Berkefeld candle. Water can be assured to be non-pyrogenic by single distillation with suitable apparatus, preferably a still equipped with a baffle plate spray catcher, if it is immediately sterilized and absolutely sealed. Precautions in all phases of preparation of solutions must be accurate and careful. A method for preparation of suitable solutions is proposed which may become a very valuable procedure in an emergency.

However, if intravenous injections are to maintain their rightful place in therapeutics, it is essential that their development shall proceed deliberately along scientific lines in the laboratories of pharmocology, physiology, and bio-chemistry, and in properly equipped hospitals. In the past, many agents have been injected into the veins of man in a haphazard, empiric, and irrational manner. Continuance of this practice will surely bring this type of therapy into disrepute, and much value will be lost thereby.

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