INTRAVENOUS INJECTIONS OF AMINO-ACIDS (HYDROLYZED CASEIN) IN POSTOPERATIVE PATIENTS*

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IN A paper[1] before this Association two years ago, I described clinical experiences with surgical patients who received intravenous injections of a mixture of amino-acids (Amigen†) as a means of supplying protein parenterally. Evidence of its beneficial effects, both clinical and chemical, was obtained. However, the number of cases was small and the occasional occurrence of untoward reactions seemed to demand a larger experience with this new method of intravenous protein alimentation. Accordingly, a large series of injections were made on the wards of the St. Louis City Hospital. We carried out all of the injections ourselves except that when one of us (D. O. W.) entered the Medical Corps of the United States Army, Drs. L. V. Mulligan, T. C. Tyrell, and W. H. Elliott substituted for him. All patients receiving Amigen were carefully observed and records kept on a separate form. At least one of us (E. B.) was present with the patient during all injections in order to make the observations as complete as possible.

TABLE I

SUMMARY OF INTRAVENOUS INJECTIONS OF AMIGEN

Solution Contained				Surgical (Post-op.) Cases		Medical Cases			
Solution No.	Amigen (Per Cent)	Glucose (Per Cent)	Prepared by	Number of Patients	Number of Injections, (Liters)	Number of Patients	Number of Injections, (Liters)	Pyrogenic* Reactions	Deaths*
1.....	2.5	10	M. J.	2	7	49	95	10	5
2.....	2.5	10	M. J.	8	17	5	8	1	0
3.....	2.5	10	B. H.	42	97	20	30	0	0
4.....	2.5	5	B. H.	23	39	21	26	0	2
5.....	2.5	2.5	M. J.	66	514	3	6	3	10
6.....	2.5	2.5	B. H.	55	100	15	18	1	3
7.....	5	5	M. J.	2	36	1	11	0	0
Totals..				198	810	114	203	15	20

* No pyrogenic reactions or deaths were due to Amigen (see text).

Procedure.—Preparation of Solutions: Amigen is an impalpable, nearly white powder which in water forms a clear, amber-colored solution with a pH

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† The amino-acids used were a mixture (containing also some polypeptides) made by the enzymic hydrolysis of purified casein and prepared and supplied by Mead-Johnson and Company; it is called, and will be referred to as "Amigen."

of 4.5. Various solutions were used in the present study. Their composition is listed in Table I. In general, two methods were used for sterilization. The solutions prepared in Barnes Hospital (B. H.) were passed through a single Berkefeld filter, autoclaved at five pounds pressure for 30 minutes and used soon thereafter. The solutions made by Mead-Johnson and Company (M. J.) were subjected to careful Seitz filtration, but not autoclaved; their sterility was carefully tested before use.

As is well known, many febrile reactions with chills are due to the use of distilled water containing pyrogens. These pyrogens are products of bacterial growth which may occur even in distilled water which is allowed to stand for any length of time either in a container or in some undrained portion of the apparatus which is not sterile. Freshly distilled water coming directly from the condenser of properly designed stills, is not pyrogenic; such water was employed in the preparation of all solutions used in the present study, with one exception. The first batch used (Solution No. 1) was inadvertently made up with distilled water which was later found to be pyrogenic. It is notable that ten of the total of 15 reactions, indeed all which could be explained in no other way, occurred with this solution. This defect was, of course, immediately corrected; subsequent solutions were not only made with freshly distilled water, but tested for pyrogens by injection into rabbits.

Selection of Cases.—No attempt was made to select special cases in this study except that most of them were surgical patients. The medical and surgical diagnoses are listed in Table II. Nearly all of the patients were dehydrated and ill and needed parenteral fluids; many of them were in a critical

TABLE II

DISTRIBUTION OF CASES

	Number of Patients	Number of Injections
Surgical (postoperative):		
Acute appendicitis, mostly with peritonitis	52	201
Intestinal obstruction, mostly due to cancer	15	119
Perforated peptic ulcer, many with severe peritonitis	12	102
Gastrectomy, mostly for cancer	7	85
Exploratory celiotomy, mostly for cancer	12	57
Herniotomy, mostly ventral	19	67
Fractures	39	65
Cholecystectomy	9	53
Burns	4	10
Miscellaneous	29	51
Totals	198	810
Medical:		
Pulmonary tuberculosis	43	56
Senility	24	36
Cardiac disease and hypertension	12	41
Pneumonia	10	19
Alcoholism	3	4
Arthritis	7	12
Miscellaneous	15	35
Totals	114	203
Grand Total	312	1013

condition at the time of injection. They represented, in general, a fairly representative cross-section of the indigent found in a large city hospital.

Rate of Injection.—In general, an average rate of 300 to 500 cc. per hour (about 5 to 8 cc. per minute) was maintained. With solutions containing 2.5 per cent of amino-acids, the amount injected in an hour was, therefore, roughly, 8 to 12 Gm. If this rate were continued for 24 hours, between 200 and 300 Gm. of protein nourishment could be thus administered, although the volume (8 to 12 liters) would be excessive. In a few cases the rate was greater, up to 500 and 900 cc. per hour of the 2.5 per cent solution. The largest amounts of Amigen were given as 5 per cent solutions (see No. 7, Table I). In two of these patients, 300 Gm. of Amigen (with equal amounts of glucose) were injected each day for three days, by means of a continuous venoclysis. Recently, a patient inadvertently received 1,000 cc. of 10 per cent Amigen in less than an hour; however, it had been neutralized to a pH of 6.5 by the addition of NaOH. Aside from abdominal pain, nausea, and vomiting there was no untoward result of this excessive rate of injection.

Most patients received but one or two liters of the Amigen solution. The most seriously ill were given more; the largest amount given to one patient was 26 liters during the course of ten days. In the two patients mentioned above, six liters a day were given for three consecutive days. We are unable to say how much more Amigen can be given per day as no attempt was made to increase the dose already mentioned, except that recently a patient received 25 Gm. of neutralized Amigen per hour for eight hours, with no reaction and considerable clinical benefit. Experimentally, we have injected without reaction as much as 140 Gm. of Amigen to a 10-Kg. dog in 24 hours, with insignificant loss of amino-acids in the urine; this would correspond to 980 Gm. in a 70-Kg. adult, or about 40 Gm. per hour, which is three to five times the rate we used in patients.

Findings.—The clinical effects of the Amigen injections were carefully observed in each case and detailed records made thereof. Table I shows the general distribution of some of the data.

Pyrogenic Reactions: Although chills and fever occurred in 15 instances, as can be seen by consulting Table I, ten of them occurred in patients receiving Solution No. 1; as already mentioned, this was the first solution employed and contained pyrogens in some of the distilled water used in its preparation. Of the remaining instances, three occurred in two medical patients, one with an acute respiratory infection, the other a severe osteo-arthritic; both patients had had chills previously. Of the remaining two instances, both had chills but no fever and thus really should not be classed as pyrogenic reactions. On the other hand, at least one of the patients in this series had chills and fever following a transfusion before receiving Amigen. From this analysis, it seems fair to conclude that the few observed pyrogenic reactions (chills and fever) were not produced by Amigen, and that solutions which are not pyrogenic produce no reactions on the addition of Amigen thereto.

Other Reactions: Two instances of urticaria were observed, one in a pa-

tient known to be allergic to various substances. Since allergy may be due to nonprotein materials, we may explain these two instances on such a basis, *i.e.*, to amino-acids or possibly mineral elements in the hydrolyzed casein. In both patients, the skin lesions responded to adrenalin and were followed by no sequelae. Flushing of the skin occurred in several patients, probably due to the specific dynamic effect of the amino-acids, which has been noted by other observers. As to temperature elevations, most of our patients were already suffering from fever before the amino-acids were injected, or were expected to develop fever as a result of the operative procedure. Study of these cases failed to show that Amigen was responsible for any significant temperature elevations. In many instances, the known specific dynamic action of the amino-acids, themselves, may have provoked some fever inasmuch as Shohl and Blackfan[2] found that the temperature elevations produced in infants by pure crystalline amino-acids and by hydrolyzed casein were alike. The chilly sensations observed in a few cases were, perhaps, also due to a specific dynamic action. Indeed, in two out of three cases in which the test was made, the basal metabolic rate increased during the course of the Amigen injections. Nausea and vomiting were rare in the present series; indeed, when expected as postoperative manifestations, Amigen seemed to minimize them. However, such symptoms are associated with the rate of injection; when Amigen is injected rapidly abdominal pain, nausea, and vomiting have been observed by Farr, Emerson, and Futcher.[3] In the patient mentioned above who received 100 Gm. in less than an hour, these symptoms occurred, though there were no other untoward effects.

Phlebitis: Careful observation revealed no instance in which 2.5 per cent Amigen caused any more phlebitis than similar solutions containing glucose alone. More recently we have prepared a neutralized Amigen solution (pH=6.5) which in stronger concentrations (5 and 10 per cent) seems less likely to produce phlebitis than similar solutions at a pH of 4.5.

Deaths: Careful analysis of the deaths in this series of cases revealed no instance in which the Amigen could have been responsible. In each case the patient was in a critical condition before the administration of the amino-acids. They were given in these patients because they proved of such definite help in other similar cases which recovered. These were patients with serious gastro-intestinal disease, in poor nutritional and general condition, a situation which is not uncommon among the indigent.

Therapeutic Value: Detailed objective evidence that amino-acids, when given intravenously, have a definite therapeutic value, was published in a previous paper from this clinic.[1] It was shown, for example, that excellent utilization of the injected material was achieved first because nitrogen retention was marked and persisted even during two weeks of therapy and second, because significant increases of the plasma protein concentration took place. Such detailed observations were not made in the present study. However, from the purely clinical point of view, there was ample evidence of the beneficial, even dramatic, effects of Amigen. In many cases it seemed clear that

the addition of the amino-acids to the parenteral glucose, after serious operations, tipped the balance in favor of recovery, although such impressions are, of course, difficult to prove. Significant was the fact that many patients volunteered expressions of subjective improvement in their general sense of well-being and strength, and this was confirmed by their clinical appearance and by the usual bedside observations.

It might be well, at this point, to make a few general remarks concerning the subject of protein deficiency. The practical application of this new method of parenteral protein therapy will be realized to a large extent by our ability to recognize protein deficiencies in surgical patients. The value of glucose is taken for granted because it supplies calories; yet body fat and tissue protein can likewise supply calories.

But there is no substitute for protein; indeed, one might say that if there is any secret of life it is bound up with protein which is the basis of all living protoplasm. In the past we have been lulled into a false sense of security about protein needs because of the presumed "stores" of protein in the body. Recent evidence has cast doubt on the practical application of this assumption. For example, it is now known that depletion of plasma albumin begins immediately after protein intake is stopped. Indeed, though hypoproteinemia is the only protein deficiency which can be recognized and measured clinically, its frequency is now generally admitted. Undoubtedly, other tissues suffer when their protein is depleted. The liver comes to mind, and something is known of this.[4, 5, 6, 7] Manifestations of protein deficiency in other organs will doubtless be detected as time goes on. Indeed, one may even go further and say that certain acute conditions, such as burns, severe hemorrhage, shock, *etc.*, are in reality examples of acute protein deficiency since they lead to acute hypoproteinemia which the body cannot correct rapidly enough, and because fluid containing protein (plasma) is so therapeutically effective.

Plasma as a protein-containing fluid has become widely recognized within recent years as an important method of replacing lost protein, though it was used first in severe burns[8] at the St. Louis City Hospital in 1935. As a means of supplying protein nourishment, though plasma leads to positive nitrogen balance in humans as shown by Kremen, *et al.*,[9] it has two possible disadvantages. First are practical limitations; for example, the largest amount of protein which was given in 24 hours in the present study (300 Gm.) would require over 4,000 cc. of plasma or at least 16 donors a day. Second, are theoretical factors, *i.e.*, plasma replaces lost protein in the blood only, but must be hydrolyzed to amino-acids or small polypeptides by the body before it can be utilized by other tissues. In contrast, amino-acids injected intravenously are immediately available to all issues. Indeed, if protein synthesis is rapid and much evidence seems to indicate that it is, an appropriate mixture of amino-acids should be built up into plasma proteins quickly enough to supplant in part, at least, the need for plasma and transfusions even in acute conditions, such as severe burns and hemorrhage. Work along this line is now in progress.

SUMMARY

Observations have been made of the injection of 1,013 liters of glucose solution containing a mixture of amino-acids (Amigen) in 312 patients. The injections were well tolerated and gave ample evidence of clinical benefit. Only two instances of urticaria were observed. The intravenous injection of a properly prepared solution of suitably hydrolyzed casein into the human in amounts averaging 8 to 12 Gm. per hour for an average-sized adult is a safe procedure, and is the most simple and convenient way of supplying large amounts of protein nourishment parenterally. The far-reaching implications of this new method of therapy are briefly discussed.

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