

REACTION IN DEMENTIA PRÆCOX TO THE IN- TRAVENOUS ADMINISTRATION OF NON- SPECIFIC PROTEIN.*

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In view of the tendency noted in dementia præcox for remission following acute febrile infections,¹ it was deemed that it might prove of some value to study the reaction, from this standpoint, in a group of such cases, to the intravenous exhibition of non-specific (bacterial) protein, which, it has been determined, exerts much the same general constitutional effect, and, being wholly controllable, may be regarded as essentially danger free. This was done somewhat in extenso, so as to allow for the possibility of added contribution to the general systemic effect of foreign protein, parenterally introduced, a question which has, as yet, been by no means completely settled. Such a study was regarded as of especial interest in view of the contradictory results reported by certain workers with reference to the response, in dementia præcox, to the subcutaneous administration of sodium nucleinate, a non-bacterial protein which is known to induce hyperthermia and leukocytosis. Thus Itten² and Kraepelin,³ utilizing this reagent, were absolutely unable to detect any evidence suggestive of psychic amelioration, while Donath⁴ claims definite improvement in eight, and recovery in four, of a series of fourteen cases, and Lundval,⁵ employing a solution containing sodium nucleinate, arsenious acid and hetol, reports apparent recovery in six of eighteen cases.

PROCEDURE.

In this investigation, a series of seven male cases was studied (Table I), including well-marked representatives of the four

TABLE I.—CASES.

Case.	Number.	Age.	Sex.	Type.	Years duration.	Stage.
1—C. S.....	18,070	30	Male.	Paranoid.	1	A.
2—V. H. M....	18,266	26	Male.	Hebephrenic.	3	A.
3—L. H.....	18,374	20	Male.	Hebephrenic.	4	A.
4—H. S.....	16,702	28	Male.	Hebephrenic.	10	B.
5—Z. F. A....	17,686	35	Male.	Simplex.	5+	B.
6—A. W.....	13,295	35	Male.	Hebephrenic.	14	C.
7—G. T.....	7,707	56	Male.	Catatonic.	22	C.

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primary types of dementia præcox, all of whom were otherwise clinically negative.

The cases were, in addition, so selected as to render possible a survey over patients in three successive stages in the progression of the disease. Thus, the cases included under A were those of relatively brief clinical duration, showing confusion and definite lack of adjustment, *i. e.*, acute phase; the cases included under B were those of longer duration, somewhat adjusted, and showing a certain degree of deterioration, *i. e.*, subacute or chronic phase; and the cases included under C were those of very long duration with profound deterioration, *i. e.*, terminal phase.

The bacterial protein used was typhoid vaccine (Parke-Davis) which has apparently come to be regarded as the agent of choice in general non-specific protein therapy.* The material was administered intravenously, as indicated (Table II) in two succes-

TABLE II.—INJECTION SCHEDULE.

Course 1.		Course 2.*	
Date.	Dosage.	Date.	Dosage.
I-11.....	500 mil.	2-17....	500 mil.
I-15.....	750 "	2-19....	500 "
I-20.....	750 "	2-22....	750 "
I-24.....	1 bil.	2-24....	750 "
I-27.....	1 "		
I-29.....	1 "		

* Cases 1 and 4 omitted from this course.

sive courses, of six and four injections, respectively, with an interval of nineteen days. The initial dosage was 500,000,000 killed bacilli which was gradually increased to 1,000,000,000, the generally recognized therapeutic maximum. The individual injections, in each course, were made at intervals of from two to five days, the vaccine being delivered from a regulation tuberculin syringe and care being taken to discharge the material very slowly (one to two minutes).

RESULTS.

The general clinical response was essentially as noted, in non-psychotic cases, by Cowie and Calhoun⁷ and others, thus malaise, occasional chill, headache, hyperpyrexia, and leucocytosis. The temperature (rectal) showed, uniformly, a marked and abrupt rise (Table III) of from 2° to 5° F. which seems to have decreased

TABLE III.—TEMPERATURE AND LEUCOCYTIC REACTION.
FIRST COURSE.

Date.	1-10-21.			* 1-11-21.			1-12-21.			1-13-21.			1-14-21.			* 1-15-21.			1-16-21.		
	Temp.		Leuc.	Temp.		Leuc.	Temp.		Leuc.	Temp.		Leuc.	Temp.		Leuc.	Temp.		Leuc.	Temp.		Leuc.
	6 A. M.	4 P. M.		6 A. M.	4 P. M.		6 A. M.	4 P. M.		6 A. M.	4 P. M.		6 A. M.	4 P. M.		6 A. M.	4 P. M.		6 A. M.	4 P. M.	
<i>Case.</i>																					
1—C. S...	98.6	99.2	11,500	98.4	103.2	17,300	102.0	99.0	8,500	98.6	100.0	9,900	100.0	99.0	6,500	98.6	101.6	12,500	100.0	98.6
2—J. H. M.	99.0	98.0	10,400	98.8	104.0	4,800	103.0	101.0	11,000	100.6	100.0	10,900	99.6	98.6	11,300	98.6	104.2	8,400	100.2	98.0
3—L. H...	98.6	99.6	7,800	98.8	101.8	9,000	98.6	100.0	5,400	99.6	98.8	5,900	99.0	98.6	4,400	98.6	100.6	9,600	100.6	98.8
4—H. S...	98.6	99.0	11,800	99.2	103.4	7,200	102.2	100.4	9,600	98.6	99.0	12,500	98.6	98.6	5,500	98.6	103.0	9,400	102.6	99.0
5—Z. F. A.	98.6	98.6	10,000	98.6	98.2	7,700	98.6	99.9	8,500	98.6	99.0	6,700	98.6	99.0	9,100	99.2	100.8	6,000	103.0	101.0
6—A. W...	99.0	98.8	9,000	98.6	102.4	17,200	101.4	100.6	9,500	100.0	98.0	8,200	98.6	98.6	6,300	98.6	101.0	9,000	99.6	98.6
7—G. T...	99.0	12,200	100.0	100.0	10,700	101.2	100.0	11,400	99.0	100.2	5,700	98.6	98.6	4,500	98.6	101.0	6,100	101.6	98.8
Date.	1-17-21.			1-18-21.			1-19-21.			* 1-20-21.			1-21-21.			1-22-21.			1-23-21.		
	Temp.		Leuc.	Temp.		Leuc.	Temp.		Leuc.	Temp.		Leuc.	Temp.		Leuc.	Temp.		Leuc.	Temp.		Leuc.
	6 A. M.	4 P. M.		6 A. M.	4 P. M.		6 A. M.	4 P. M.		6 A. M.	4 P. M.		6 A. M.	4 P. M.		6 A. M.	4 P. M.		6 A. M.	4 P. M.	
1—C. S...	98.6	98.8	13,400	98.6	98.4	10,300	98.6	98.4	6,300	100.0	98.8	15,400	98.6	98.6	13,200	98.6	99.2	13,000	99.0	98.8
2—J. H. M.	98.6	98.4	8,100	98.6	98.8	7,600	98.6	98.4	5,900	98.6	101.4	18,300	98.6	98.6	11,000	98.6	98.0	8,800	98.4	98.8
3—L. H...	98.6	99.0	6,000	99.0	98.8	3,800	98.6	98.4	9,900	98.6	102.0	12,200	99.6	98.6	6,600	98.6	98.6	4,600	98.6	98.4
4—H. S...	98.6	98.6	8,600	98.6	98.8	10,000	98.6	98.8	10,400	98.6	102.0	17,500	99.0	98.6	11,500	98.6	98.8	9,000	98.4	98.8
5—Z. F. A.	101.0	100.0	8,400	98.6	99.6	7,900	99.6	100.4	7,800	99.2	102.0	5,800	98.6	98.6	9,800	98.6	98.6	6,900	98.6	99.2
6—A. W...	98.6	97.8	7,800	98.6	98.0	12,500	97.0	98.6	7,500	98.6	100.6	11,800	98.6	98.4	8,900	98.6	98.6	11,000	98.6	96.8
7—G. T...	98.6	98.6	6,300	98.6	99.0	8,800	98.6	98.8	15,800	98.6	100.0	10,900	99.0	98.8	7,000	98.6	99.0	8,000	98.4	98.8

* Injection days.

TABLE III.—TEMPERATURE AND LEUCOCYTIC REACTION.—CONTINUED.
First Course.—Continued.

Date.	● 1-24-21.		1-25-21.		1-26-21.		* 1-27-21.		1-28-21.		* 1-29-21.		1-30-21.	
1—C. S.	98.0	14,100	98.6	98.6	8,800	98.4	99.0	10,000	98.8	99.2	22,000	98.2	99.0	98.6
2—J. H. M. . . .	98.6	100.2	98.6	98.6	9,000	98.4	96.6	8,600	98.0	99.6	10,100	98.6	99.0	98.6
3—L. H.	98.4	102.6	98.6	98.0	6,300	98.2	98.6	6,800	98.6	99.0	10,700	98.4	99.0	98.4
4—H. S.	98.6	100.8	98.0	98.6	9,000	98.6	98.0	10,700	98.6	99.0	15,800	98.6	100.8	98.4
5—Z. F. A. . . .	98.4	100.0	98.0	98.6	17,200	98.0	96.6	6,800	98.2	100.4	8,400	98.4	99.2	98.8
6—A. W.	98.0	100.8	98.0	98.0	8,700	98.0	98.2	6,700	98.0	100.0	9,900	98.0	99.2	98.6
7—G. T.	98.4	101.0	98.6	98.4	8,000	98.0	98.6	7,700	98.2	99.4	8,000	98.2	99.0	98.0

SECOND COURSE.

Date.	2-15-21.	2-16-21.	* 2-17-21.	2-18-21.	* 2-19-21.	2-20-21.	2-21-21.
2—J. H. M.	98.2	98.6	98.2	98.6	102.8	98.6	98.8
3—L. H...	98.4	98.6	98.2	98.4	101.0	99.0	98.4
5—Z. F. A.	98.8	98.8	98.4	98.2	101.0	98.6	99.0
6—A. W...	98.2	98.2	98.2	98.8	102.8	98.8	98.8
7—G. T...	98.6	98.6	98.4	98.4	101.2	98.6	98.4

Date.	* 2-22-21.	2-23-21.	* 2-24-21.	2-25-21.
2—J. H. M.	98.4	98.6	101.2	99.0
3—L. H...	98.6	98.6	100.4	99.6
5—Z. F. A.	98.2	98.4	103.4	98.6
6—A. W...	98.6	98.6	102.4	98.8
7—G. T...	98.6	98.6	100.6	98.6

* Injection days.

progressively as the number of injections was increased. There was also remarked, as indicated, a very definite leukocytosis (Table III) which, however, seems to have been somewhat lower than observed by Cowie and Calhoun.' It seems, too, from Table IV, in which the initial count was made 48 hours following the first injection of the second course, that the preliminary leucopenia described by Cowie and Calhoun' was, in our cases, consistently

TABLE IV.—CHRONOLOGIC ANALYSIS OF LEUCOCYTIC REACTION.

Time.	Leucocyte counts.						
	$\frac{1}{2}$ hour before inject.	$\frac{1}{2}$ hour after inject.	1 hour after inject.	2 hours after inject.	3 $\frac{1}{2}$ hours after inject.	5 $\frac{1}{2}$ hours after inject.	7 $\frac{1}{2}$ hours after inject.
Case.							
2—J. H. M..	6,400	10,800	7,200	9,199	7,500	7,800	11,400
3—L. H....	6,700	7,000	5,600	11,400	9,800	9,900	10,700
5—Z. F. A..	3,800	8,000	3,700	8,200	8,500	3,700	3,200
6—A. W....	7,000	11,000	7,900	12,400	15,100	9,600	9,000
7—G. T.....	5,100	7,100	7,400	13,500	8,800	7,600	6,600

Time.	Leucocyte counts.						
	9 $\frac{1}{2}$ hours after inject.	12 hours after inject.	24 hours after inject.	33 hours after inject.	48 hours after inject.	55 hours after inject.	72 hours after inject.
Case.							
2—J. H. M..	10,200	10,500	7,800	6,800	5,800	7,400	8,800
3—L. H....	7,200	6,700	5,400	7,900	3,000	9,000	8,700
5—Z. F. A..	8,200	7,200	6,700	6,600	2,600	5,600	5,400
6—A. W....	14,600	14,800	7,800	6,700	5,700	8,000	10,800
7—G. T.....	7,000	7,200	6,700	6,300	6,900	7,600	9,200

preceded by a short period of mild leucocytosis, and in addition, that the second or essential leucocytic period, which seemed to reach its acme in approximately 12 hours was succeeded by a phase of gradual reduction with the establishment of definite leucopenia in about 48 hours, following which there seemed to be gradual return to the normal level.

In regard to the effect upon the red cells (Table V), there was uniformly noted a severe reduction in the total red count, so much so that it was deemed advisable to drop two of the cases (1 and 4) from the second course. This reduction was a prolonged nature,

TABLE V.—BLOOD PICTURES.

Case.	Preceding first course.							On completion of first course.										
	Erythrocytes.	Leukoocytes.	Poly. Neutro.	Large Lymph.	Small Lymph.	Transitional.	Myelocytes.	Eosinophiles.	Basophiles.	Erythrocytes.	Leukoocytes.	Poly. Neutro.	Large Lymph.	Small Lymph.	Transitional.	Myelocytes.	Eosinophiles.	Basophiles.
1—C. S.	3,960,000	11,500	74	8	25	6	0	0	0	3,570,000†	8,200	66	12	11	7	0	0	0
2—J. H. M.	4,480,000	10,400	55	12	25	6	0	2	0	3,490,000	7,500	62	4	26	8	0	0	0
3—L. H.	5,280,000	7,800	73	5	17	4	0	1	0	3,500,000	4,900	75	3	16	3	0	3	0
4—H. S.	4,240,000	11,800	65	9	20	2	0	4	0	3,570,000	8,400	59	13	16	8	0	4	0
5—Z. F. A.	5,680,000	10,000	69	7	14	4	0	5	0	4,200,000	7,100	72	3	13	4	0	2	1
6—A. W.	4,740,000	9,000	56	5	32	6	1	0	0	4,050,000	7,400	63	8	24	5	0	0	0
7—G. T.	4,900,000	12,200	73	7	14	5	1	0	0	3,940,000	7,900	75	3	16	5	0	1	0
	Preceding second course.							On completion of second course.										
1—C. S. †....	2,500,000	11,800	63	3	23	4	0	0	1	3,250,000	10,400	73	0	22	4	0	1	0
2—J. H. M.	4,310,000	10,000	80	2	11	6	0	1	0	3,680,000	6,600	79	0	20	1	0	0	0
3—L. H.	4,100,000†	5,200	55	5	32	6	0	2	0	3,560,000	8,300	69	4	26	1	0	0	0
4—H. S. †....	2,860,000*	14,600	73	2	20	3	0	2	0	3,850,000	9,600	75	19	4	0	0	2	0
5—Z. F. A.	4,020,000	8,000	71	4	23	2	0	0	0	4,180,000	7,500	86	2	8	3	0	1	0
6—A. W.	3,270,000	11,600	68	3	27	1	0	1	0	3,630,000	9,000	69	1	28	1	0	1	0
7—G. T.	3,500,000	9,800	71	3	24	2	0	0	0	4,230,000	7,800	59	1	35	2	0	2	1
	8 weeks following first course.																	
1—C. S.	3,840,000	5,100	84	0	10	3	0	0	0									
2—J. H. M.	2,480,000	12,200	78	0	16	1	0	5	0									
3—L. H.	3,470,000	5,200	63	3	24	4	0	4	2									
4—H. S.	3,700,000	8,600	68	1	28	2	0	1	0									
5—Z. F. A.	3,530,000	6,600	60	1	27	6	0	6	0									
6—A. W.	4,000,000	4,000	60	0	28	1	0	0	1									
7—G. T.	3,500,000	5,200	83	0	13	4	0	0	0									

* Many macrocytes, microcytes, and poikilocytes.
† Many platelets.
‡ Omitted from second course.

* Many macrocytes, microcytes, and poikilocytes.

† Many platelets.

‡ Omitted from second course.

persisting in these two cases for at least eight weeks, and in the others for at least four. Increased platelet count, as described by Cowie and Calhoun,⁷ was occasionally noted as well as the appearance in one case, in unusual numbers, of macrocytes, microcytes, and poikilocytes. No frank change, however, was noted as regards white cell type.

Determination of erythrocyte fragility (Butler⁸ as modified by Greenthal,⁹) showed (Table VI) moderate increase in fragility

TABLE VI.—BLOOD FRAGILITY.

Case.	Date.	Fragility curve.	Date	Fragility curve.	Date	Fragility curve
1—C. S....	2-18-21	0112345555	2-25-21	0012355555	3-18-21	0012455555
2—J. H. M.	2-18-21	0001234555	2-25-21	0000123555	3-18-21	0001345555
3—L. H...	2-18-21	0001234555	2-25-21	0001235555	3-18-21	0001345555
4—H. S....	2-18-21	0001234555	2-25-21	0001234555	3-18-21	0001245555
5—Z. F. A.	2-18-21	0112345555	2-25-21	0001345555	3-18-21	0011355555
6—A. W...	2-18-21	0012344555	2-25-21	0001235555	3-18-21	0000145555
7—G. T....	2-18-21	0012345555	2-25-21	0001234555	3-18-21	0001345555
Normal Curve...		0001234555				

Key: 0—no hemolysis. 2—trace of hemolysis. 4—almost complete hemolysis.
1—faint trace of hemolysis. 3—partial hemolysis. 5—complete hemolysis.

in two cases (1 and 5) and slight increase in two others (6 and 7), which in all cases, except the first, was apparently of but short duration.

Examinations of the urine revealed no evidence suggestive of renal disturbance nor was there indication of essential physical change save for a gradual decrease in weight (Table VII), asso-

TABLE VII.—WEIGHTS.

Case.	Date.	Wt.	Date.	Wt.	Date	Wt.	Date.	Wt.
1—C. S.....	1-7	129	1-14	125	1-21	118	1-28	134
2—J. H. M.....	1-7	115	1-14	112	1-21	114	1-28	119
3—L. H.....	1-7	141	1-14	141	1-21	134	1-28	139
4—H. S.....	1-7	178	1-14	178	1-21	163	1-28	176
5—Z. F. A.....	1-7	145	1-14	144	1-21	138	1-28	146
6—A. W.....	1-7	118	1-14	112	1-21	114	1-28	114
7—G. T.....	1-7	132	1-14	132	1-21	132	1-28	135
1—C. S.....	2-4	133	2-11	133	2-18	133	2-25	133
2—J. H. M.....	2-4	119	2-11	116	2-18	113	2-25	117
3—L. H.....	2-4	143	2-11	144	2-18	138	2-25	142
4—H. S.....	2-4	181	2-11	182	2-18	180	2-25	185
5—Z. F. A.....	2-4	149	2-11	147	2-18	141	2-25	145
6—A. W.....	2-4	119	2-11	118	2-18	115	2-25	117
7—G. T.....	2-4	138	2-11	135	2-18	135	2-25	133

ciated with transient asthenia, which continued until about the midpoint of the first course, soon thereafter reattaining its original level, which was well maintained until the completion of the study and, in fact, in two cases, showed an appreciable increase.

Psychiatrically, there was absolutely no evidence indicative of remission or even transitory improvement although, in certain cases, (A and B types) there was noted for several days, towards the end of the first course, a certain cheerfulness and good humor which might possibly be construed as approximating the euphoria of the second or positive phase, more or less characteristically noted by Petersen,¹⁰ as following the administration of non-specific protein. Although it is theoretically conceivable, had treatment been continued over a longer period of time, that definite improvement might have been effected, yet in view of the direct nature of the procedure, the vigor of the reaction and the length of period actually employed, such a possibility seems rather unlikely.

It appears therefore that the results of this study are in general agreement with those of Itten and Kraepelin (*loc. cit.*) and definitely at variance with those of Donath and Lundval (*loc. cit.*). However, as concerns the findings of the authors last mentioned, whose cases were treated and observed over a number of years, due regard must be accorded the fact that much of the apparent improvement remarked, might, possibly, have occurred per se and need not, of necessity, have been specifically induced by the nucleinate injections.

SUMMARY.

It seems, in the dementia præcox cases constituting this series, that no amelioration in psychiatric status was effected as a result of the intravenous administration of non-specific bacterial protein, and that the general constitutional reaction, in these cases, closely approximated that reported as characteristic of non-psychotic individuals, save, that in the former, there seems to have been, additionally, evidence of transient weight-loss, a preliminary leucocytosis period, a late leucopenic period, and a marked persistent reduction in the erythrocyte count with a tendency for increased fragility changes, all of which, upon further study, may be found to be typical of non-psychotic cases as well.

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