THE EFFECT OF ALTERING THE CONDITIONS OF THE AUTONOMIC NERVOUS SYSTEM ON THE CHOLINE ESTERASE LEVEL IN HUMAN BLOOD SERUM.

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WITHIN recent years a great deal of attention has been paid to the question of chemical transmission of nervous impulses, and it has been definitely established by Dale and his co-workers (1, 2, 3) that acetyl choline is the transmitter in the case of the parasympathetic nervous system, and also in part of the sympathetic nervous system.

It is impossible to get any direct quantitative measure of the acetyl choline content of human tissues, but the acetyl choline formed in the body is destroyed by a change enzymic in nature. This point has been investigated by Stedman and Stedman (4, 5), and Ammon and his co-workers (6, 7), who have suggested that the enzyme is specific and called it choline esterase.

Using the method of estimating the choline esterase content of human blood sera described in a previous paper (8), a group of thirty normal controls was investigated. The figures obtained showed a range of from 52 to 114 units (μl CO_2 per minute per ml. of serum) at 37° C., with an average of 83 units. Further investigations carried out with a view to establishing any variance determined by food, exercise, sleep, etc., showed remarkably consistent results, the figures invariably remaining constant. Moreover, on keeping the serum several days, no alteration in the choline esterase level was found. As acetyl choline is so intimately concerned with the transmission of nervous impulses in the autonomic nervous system, it seemed desirable to investigate the level of serum esterase in conditions where autonomic imbalance could be demonstrated clinically. A large group of neurotic and psychotic cases, 142 in all, were investigated (see Table I).

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TABLE I.

Diagnosis.	Number of cases.
Anxiety states.	25
Hyperthyroidism	9
Hysteria	6
Manic-depressive psychosis . . .	20
Involutional depression	29
Schizophrenia	13
Senile psychoses	8
Paranoia and paraphrenia . . .	4
Epilepsy	7
Post-encephalitics	2
Others, including endocrinopathies, puerperal insanity, narcolepsy, enuresis, etc. .	19
Total number of cases investigated .	142

Of these cases, 36 were outside the limits obtaining in the so-called normal group; 20 were above the upper limit of normality; of these, 7 were severe anxiety neurotics, 3 were agitated depressives, 3 were manics, 2 were cases of exophthalmic goitre, and the remaining 5 were made up of a vagotonic, an enuretic, a paraphrenic, a hysteric and a case of adrenal cortical hyperplasia. Of the 16 cases with the choline esterase figure below 52 units, 5 were epileptics, 3 were melancholic stupors, 2 were catatonic schizophrenics, 2 were senile depressions, 2 were depressions, 1 was a post-encephalitic, and 1 was a case of Cushing's syndrome with definite evidence of adrenal hyperplasia, e.g. marked hypertension, diminished glucose tolerance, virilism, etc. In this latter case it is of interest to note that the original figure was 104 units, but following two operations, as the result of which the sympathetic nerve supply to the adrenals was cut, the figure dropped to 52 units.

It is quite apparent that these two groups represent entirely different material when considered from the point of view of their autonomic status. In the first group, anxiety with its somatic accompaniments was present in practically every case. In the second group, evidences of autonomic over-activity were entirely absent, and 9 of the cases showed either stupor or a state of dementia where volition was entirely lacking. It was now decided to ascertain what drugs, if any, were effective in altering the choline esterase level in any one case. In this connection, marked inhibition of the choline esterase figure in a group of 12 patients was obtained by using eserine sulphate, gr. $\frac{1}{50}$, subcutaneously. The parasympathetic response following the administration of eserine depends on this inhibition. The figures obtained in this group of cases are shown in Table II (from previous paper, (8)).

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TABLE II.—*Response to Eserine.*

Case.	Age.	Diagnosis.	Choline esterase. Before eserine.	Choline esterase. After eserine.	Variation.
1	62	Paranoia	99	81	−18
2	38	Schizophrenia	78	66	−12
3	48	Agitated depression	81	68	−13
4	56	Involutional melancholia	26	19	−7
5	52	Agitated depression	75	56	−19
6	47	Involutional melancholia	66	56	−10
7	21	Melancholia	70	54	−16
8	18	Melancholic stupor	53	55	+2
9	41	Anxiety state	80	63	−17
10	37	,, ,,	81	68	−13
11	44	Paranoia	54	44	−10
12	55	Disseminate sclerosis	93	78	−15

The limit of experimental error is of the order of 2 units.

TABLE III.—*Response to Prostigmine.*

Case.	Choline esterase. Before drug.	Choline esterase. After drug.	Variation.
1	76	37	−39
2	31	10	−21
3	83	35	−48
4	83	41	−42
5	70	54	−16

Second sample of blood removed 2 hours after 2 c.c. of prostigmine.

With prostigmine, 1 mgrm. subcutaneously, similar results were obtained (see Table III). In this connection it is interesting to note that Stedman (9) has investigated the choline esterase level in the serum of patients suffering from myasthenia gravis and found that the values tend to be low. This excludes any simple explanation of the therapeutic action of prostigmine in myasthenia, and the benefit resulting from the use of prostigmine in this condition does not appear to depend upon the prevention of an excessive destruction of acetyl choline by the esterase. However, the results obtained with eserine and prostigmine simply demonstrate a temporary inhibition of the esterase, which lasts for a few hours, the figure then returning to the previous level. In an attempt to produce a more permanent change in the level of choline esterase in the blood, prolonged stimulation of the parasympathetic nervous system with carbaminoylcholine chloride (Doryl, Merck)

was tried. This drug has an action similar to acetyl choline, but is destroyed less quickly by the body and its action is, therefore, more prolonged. It was found that the esterase figure was unaltered by a single dose of doryl sufficient to produce somatic indication of parasympathetic activity, such as sweating and frequency of micturition, but was increased by administration of doryl over a period of weeks (see Table IV).

TABLE IV.—*Response to Carbaminoylcholine Chloride.*

Case.	Choline esterase. Before drug.	Choline esterase. After drug.	Variation.
1	65	79	+14
2	96	113	+17
3	87	93	+6
4	65	80	+15
5	83	94	+11
6	78	84	+6
7	74	81	+7
8	83	86	+3

Second sample of blood removed after twice daily injections of ·00025 grm. doryl for 10 days.

Clinical experience has shown that bellergal (Sandoz) is beneficial in diminishing the somatic symptoms resulting from autonomic over-activity in neurotic patients. For this reason the effect of prolonged administration of this drug upon the choline esterase activity in a group of patients was investigated (see Table V). One tablet of this drug contains bellafoline ·1 mgrm., ergotamine tartrate ·3 mgrm., phenobarbital 20 mgrm.

TABLE V.—*Response to Bellergal.*

Case.	Choline esterase. Before drug.	Choline esterase. After drug.	Variation.
1	76	57	−19
2	91	74	−17
3	111	98	−13
4	78	85	+7
5	87	61	−26

Second sample of blood removed after 1 tablet bellergal (Sandoz) given *t.i.d.* for 10 days.

Several *in vitro* experiments were carried out, using special flasks, which permitted the addition of a substance after the reaction had proceeded for

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sufficient time to calculate an activity value. Using this method, the activity after one half tablet had been added to both reaction and control flasks was approximately one half the activity before the drug was added.

The precise mechanism of this inhibition has not yet been fully elucidated, but the significance is that the decrease in esterase activity shown by the patient to whom bellergal was administered is very much greater than would be expected if the decrease was due entirely to a direct inhibitory action of the drug.

Discussion.

Any attempt to measure cholinergic activity indirectly by assuming that the choline esterase in serum varies as the production of acetyl choline at the nerve-endings is at present premature. However, when it was found, as the result of investigation of the choline esterase figures in a large group of patients, that the cases showing figures considerably higher than those of the apparently normal controls had, in practically every case, evidences of autonomic over-activity, it seemed reasonable to suppose that this autonomic activity was in some way connected with the high esterase content of the blood. Moreover, the cases showing choline esterase levels below those of the normal controls were in marked contrast to the previous group and, as already stated, 9 of the 16 cases were either in a state of stupor or, in the case of the demented patients, showing little or no movement by virtue of a complete lack of volition. Of the remaining 7, 4 were epileptic and 2 were depressives, while 1 had had an adrenal sympathectomy. Thus the evidence presented by the clinical material was in favour of the concept that the level of the choline esterase in the blood is to some degree proportionate to the state of autonomic activity. If the body responded to excessive cholinergic activity by an increase in the choline esterase activity, then this effect ought theoretically to be capable of reproduction by prolonged stimulation of the parasympathetic nervous system by drugs. The evidence from using doryl, although by no means conclusive, supports this contention.

With bellergal a definite fall in the level of choline esterase was obtained, and evidence is adduced to show that this is not wholly attributable to any direct inhibitory action of the drug. It is believed that the clinical improvement found on using this drug in neurotic cases is dependent upon its stabilizing effect upon the autonomic nervous system, and that this factor is partly responsible for the fall in the level of the choline esterase.

Unfortunately, as yet we have not had the opportunity to follow up our case material, and correlate the level of the choline esterase with alteration in the clinical state.

We have attempted in this paper to indicate a possible correlation between the choline esterase level in the blood and the clinical evidences of autonomic

activity, but fully appreciate that many other factors must be considered in this connection.

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