5-HYDROXYINDOLES IN MENTAL DEFICIENCY

BY

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During a previous investigation in which a decreased production of 5-hydroxyindoles was demonstrated in phenylketonuric patients (Pare, Sandler, and Stacey, 1957, 1959), we observed that some non-phenylketonuric mental defective patients had abnormally high serum levels of 5-hydroxytryptamine (5-HT). We have now extended our observations and tried to define the extent and significance of this finding.

Subjects and Methods

Eighty-three non-phenylketonuric mentally defective patients of all ages, drawn from four hospitals, and 68 subjects in various control groups were considered in this survey (Table I). To aid classification, questionnaires were sent to the parents of a large proportion of the patients requesting information about antenatal, perinatal, and postnatal periods.

Serum and Platelet 5-HT.—This was assayed by the methods of Hardisty and Stacey (1955) with the following modifications. Estimations were done routinely on serum because of the difficulty in transferring to the laboratory specimens of blood for platelet 5-HT estimations from patients in hospitals some distance away. The use of serum has the disadvantage that some 5-HT is lost in the red cells (Stacey, 1956). To keep variation due to this as low as possible the method of obtaining serum was standardized. Blood obtained by venepuncture was immediately put into a centrifuge tube and left in an incubator at 37° C. for 20 minutes. The clotted blood was then taken on ice to the laboratory where the serum was separated by centrifugation and 5-HT extracted with acetone. Normal values were 12% higher than those previously reported, and replicate estimations on the same blood were in good agreement.

The capacity of platelets to absorb 5-HT was measured by a method (Stacey, to be published) in which platelet-rich plasma was incubated at 37° C. for 90 minutes with excess 5-HT and in an atmosphere of 5% CO₂.

Platelet Adenosine Triphosphate.—Adenosine triphosphate (A.T.P.) was estimated in platelets by the fire-fly luminescence method of Strehler and Totter (1954) after extraction with trichloracetic acid.

Urinary 5-Hydroxyindoleacetic Acid (5-HIAA) and Creatinine.—These estimations were carried out by methods used previously (Pare et al., 1957). Overnight urine samples were used when possible, but many of the patients were incontinent and with these random specimens were used; results are expressed in terms of creatinine excretion. They will therefore only reflect the daily output of 5-HIAA if creatinine excretion is normal. No precautions were taken to control dietary intake of 5-hydroxyindoles. For these reasons less reliance can be placed on the 5-HIAA than on the 5-HT figures.

| TABLE I |
|------------------|------------------|
| **MEAN SERUM 5-HT AND URINE 5-HIAA IN NORMAL SUBJECTS, IN MENTAL DEFECTIVES, AND IN VARIOUS OTHER GROUPS** | |
| | ng. 5-HT/ml. serum | mg. 5-HIAA per g. urine creatinine |
| | Mean (No.) ± S.E. | Mean (No.) ± S.E. |
| 1 Normals | | |
| Adults | 145 (16) ± 13 | 3-9 (40) ± 0-12 |
| Children | 130 (7) ± 16 | 3-9 (18) ± 0-40 |
| 2 Cerebral palsy (normal intelligence) | 136 (12) ± 12 | 3-9 (22) ± 0-46 |
| 3 Cerebral palsy (I.Q. < 50) | 351 (28) ± 26 | 3-5 (9) ± 0-47 |
| 4 Mongolism | 146 (10) ± 18 | 7-7 (25) ± 0-73 |
| 5 Epilepsy (tuberous sclerosis) | 215 (6) ± 18 | 7-0 (10) ± 1-2 |
| 6 Phenylketonuria | 79 (26) ± 10 | 6-13 (6) ± 1-4 |
| 7 Maternal rubella | 391 (4) ± 66 | 2-6 (26) ± 0-23 |
| Various other mental defects | | |
| 8 Gargoylism | 276 (1) | 15-6 (1) |
| 9 Sturge-Weber syndrome | 367 (1) | 7-3 (1) |
| 10 "Cerebral lipidosis" | 490 (1) | 10-0 (1) |
| 11 Ichthyosis with spastic paraplegia | 120 (1) | 7-2 (1) |
| 12 Hypertelorism | 137 (1) | 6-6 (1) |
| 13 Unclassified | 297 (30) ± 24 | 6-8 (29) ± 0-47 |
| Others | | |
| 14 Epilepsy (normal intelligence) | 104 (4) ± 15 | 2-8 (4) ± 0-46 |
| 15 Schizophrenia | 89 (3) ± 12 | — |
| 16 Dementia due to anoxia | 222 (4) ± 38 | — |
| 17 Dementia due to other causes | 158 (5) ± 27 | — |

*From Pare et al. (1959).
Numbers of subjects are given in brackets. The values in italics (P < 0-05) and in heavy type (P < 0-001) are significantly different from the corresponding values for normals.

Results

Serum 5-HT and urinary 5-HIAA levels in mental defective and control groups are shown in Table I. In many cases, estimations of serum 5-HT were made on a number of occasions over several months and there was good agreement. As there was no significant difference between normal adults and children for either 5-HT (P > 0.2) or 5-HIAA (P > 1), these control groups will be considered together for purposes of statistical comparison with defective groups. The findings in the defective groups appeared to be independent of the hospital of origin, and could not be correlated with the taking of particular drugs. The case of anticonvulsant drugs is examined later.

From Table I it is apparent that in a wide variety of cases of mental deficiency the amount of 5-HT in the serum was very abnormal and that there were similar changes in the excretion of 5-HIAA.

In Cerebral Palsy.—These patients all had a symmetrical spastic paraplegia or athetosis and fell into two groups: 12 with average intelligence attending a residential school for spastics and 28 imbeciles and idiots. The mean serum 5-HT and urine 5-HIAA were normal in the patients with normal intelligence; both were considerably raised in the defectives, 26 of whom were in-patients and two out-patients. Both out-patients and all but four in-patients had a serum level of 5-HT above the normal range (100-250 ng./ml.). The mean for those with athetosis did not differ from the mean for those without it. Two cases of kernicterus had a high serum 5-HT.

In Mongolism.—Nine out of 10 cases had a normal serum 5-HT; the remaining case had 257 ng. 5-HT/ml. This child had a history of severe birth injury, he was cyanosed, and needed to be nursed in an oxygen tent for the first seven days of life. In six out of the 10 the 5-HIAA excretion was high.

In Epiloia.—In all cases the serum 5-HT was around the upper limit of the normal range; no very high values were found.

In Phenylketonuria.—These figures (quoted from Pare et al., 1959) are included for comparison and show the low serum 5-HT and urine 5-HIAA already reported.

In Maternal Rubella.—All four cases had serum 5-HT above the normal range though in only one was the urine 5-HIAA very high.

In Various Other Mental Defectives.—High values for both compounds were found in single cases of Sturge-Weber’s syndrome, gargoylism, and in a case of probable cerebral lipidosis. A single case of spastic paraplegia associated with ichthyosis has not been included with the cases of cerebral palsy as this is an overt genetic condition (Sjögren and Larsson, 1957; Richards, Rundle, and Wilding, 1957). This patient had a normal serum 5-HT as did the only case of hypertelorism investigated. The unclassified group contains all the other mentally defective cases investigated and consists of patients in whom diagnosis and aetiology were insufficiently precise to warrant inclusion in any other group. In 20 the serum 5-HT was above the normal range, in 11 within it.

For comparison with the cases of mental deficiency and in the hope that it might shed some light on the abnormalities reported above, a few other cases of gross mental abnormality were also investigated. Four out-patients of normal intelligence who were receiving large doses of anticonvulsants for major epilepsy had normal serum 5-HT and three cases of long-standing schizophrenia with gross mental deterioration somewhat low values. Four cases of dementia due to cerebral anoxia were examined. One of these, a case of mild dementia following cardiac arrest, had a normal serum 5-HT, two cases of Korsakoff’s syndrome had serum 5-HT at the upper limit of normal, and one patient with a pneumonectomy in whom a confusional state followed a severe bronchopneumonia, had a high serum 5-HT (328 ng./ml. serum). Five cases of dementia not associated with an anoxic incident included three patients with presenile dementia, of whom one had a serum 5-HT at the upper limit of normal. The others, together with one case of arteriosclerotic dementia and one of Huntington’s chorea, were all normal.

Aetiology.—Cases were classified according to whether the cause of the condition was genetic or due to damage in intra-uterine life, at birth, or in the immediate postnatal period. In well-defined clinical entities with a genetic aetiology no consistent change in serum 5-HT was found. In phenylketonuria it was low; in mongolism, hypertelorism, and the mentally defective spastic with congenital ichthyosis normal; in epiloia at the upper limit of normal; and in gargoylism, Sturge-Weber’s syndrome, and “cerebral lipidosis” high. In five of these conditions, however, only a single case was investigated.

Classification according to the time of brain damage could be made with some degree of certainty in only a small proportion of the cases, as in many either more than one aetiological factor was present or the significance of the incidents reported could not be assessed. However, from the cases

A
5-HYDROXYINDOLES IN MENTAL DEFICIENCY

where this classification could be made there appeared to be no clear difference between the level of serum 5-HT in the three groups; all contained a large proportion of patients with high serum 5-HT.

**Physical Handicap.**—Patients could be divided into those with "normal" physical functioning, in that they could walk normally, feed themselves, and within the limits of their mental deficiency and the hospital setting, lead a fairly normal life, and those with some degree of physical handicap. The second group consisted mainly of patients with central nervous system lesions giving rise to paresis, but also included those who, because of the severity of their mental defect, were unable to walk, sit up, or feed themselves in even the crudest manner.

The degree of physical handicap was graded roughly on a five-point scale:

0 = normal physical functioning
1 = slight handicap, but still able to walk without support
2 = unable to walk without support but sits unaided and uses hands purposefully
3 = sits only with support but uses hands in a purposeful manner
4 = unable to sit and makes no purposeful movements

Many cases with a high serum 5-HT had normal physical functioning. To see if there was any correlation between physical handicap and serum 5-HT it was therefore necessary to take a group as similar in other respects as possible. For this purpose 29 mentally defective spastics were grouped according to their physical handicap (Table II) and the mean serum 5-HT and 5-HIAA estimated for each group. There appeared to be no correlation between the degree of physical handicap and either serum 5-HT concentration or urine 5-HIAA/creatinine ratio.

**Intelligence.**—The difference between the findings in the mentally normal and mentally defective cases of cerebral palsy has already been referred to. In Table III two groups with physical grade 2 are compared and the difference is seen to persist. Nevertheless, when patients with different degrees of mental deficiency were compared the serum 5-HT did not appear to vary with the deficiency. The defective patients studied were mostly idiots and low-grade imbeciles and intelligence tests are necessarily inaccurate in such cases. However, with the help of Dr. R. F. Woodward, the psychologist who tested the children, 52 children at one hospital were divided into two groups: 11 more intelligent and 41 less intelligent. The mean 5-HT values for these patients were: more intelligent 293 ng./ml., less intelligent 338 ng./ml. This difference was not significant (P > 0.3).

**Symptomatic Epilepsy.**—A possible relationship between epilepsy and/or anticonvulsant drugs and serum 5-HT was also investigated. Twenty-eight mentally defective patients with epilepsy had a mean serum 5-HT of 334 ng./ml., and 37 without epilepsy had a mean of 285 ng./ml. This difference was not significant (P > 0.1).

**Nutrition.**—To investigate a possible relationship between weight and serum 5-HT, 65 defective children were divided into two groups, one of 38 whose weights were less than the third percentile for normal children (for references see Tanner, 1958) and one of 27 whose weights were above this limit. There was no significant difference between the mean serum 5-HT of the two groups (P > 0.3).

**Comparison of 5-HT and 5-HIAA.**—A comparison has been made between 5-HT and 5-HIAA within the larger groups and a positive correlation found in both the mentally normal and mentally defective cases with cerebral palsy, in epilepsy, and in phenylketonuria. The correlation was only significant, however (P < 0.05), in the group of patients of normal intelligence with cerebral palsy. In the group of mongols there was a small negative correlation which was not significant.

The between-group correlation coefficient for groups 2 to 14 in Table I, weighted by multiplying each factor by the number in the group, was 0.85; this was highly significant (P < 0.001). The means for these groups are plotted against one another in Fig. 1.

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**Table III**

<table>
<thead>
<tr>
<th>CASES OF CEREBRAL PALSY OF NORMAL INTELLIGENCE COMPARED WITH CASES WITH SIMILAR DEGREE OF PHYSICAL HANDICAP OF I.Q. &lt; 50</th>
</tr>
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<tr>
<td></td>
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<tr>
<td>-------------------------------------------------------------</td>
</tr>
<tr>
<td>Average intelligence</td>
</tr>
<tr>
<td>Mentally defective</td>
</tr>
</tbody>
</table>

* Number of patients in brackets.
defective subjects was due to a rise in blood 5-HT. This in turn can be ascribed to (1) an increased platelet count (a mean increase of 45% was observed, significant at the 5% level) and (2) each platelet containing about twice as much 5-HT as normally. This table also shows that platelets from the defective patients (when incubated with 5-HT) reached the same 5-HT content as normals. In one mongol with normal serum 5-HT, not shown in the table, platelet uptake was also not defective.

Platelet A.T.P.—In four cases in which serum 5-HT was between 310 and 440 ng./ml., platelet A.T.P. was no higher than in five normal adults.

Discussion
It is now well established that the 5-HT in serum is derived almost entirely from blood platelets and is liberated from them during clotting. However, since some 5-HT is lost in this process (Stacey, 1956), a raised serum 5-HT level could result from diminished loss. That this was not so in the cases described here has been shown by the estimation of total blood 5-HT, by the method used by Hardisty and Stacey (1955), in 10 cases taken at random from among those with a high serum 5-HT level. In all it was considerably raised and the mean for the group was nearly three times that of the mean for normal subjects. This rise was partly due to an increased platelet count but mainly to the platelets in the mentally defective patients containing on the average twice as much 5-HT as normal platelets. When the platelets were saturated by incubation

![Figure 1](http://jnnp.bmj.com/)

**Fig. 1.**—Mean serum 5-HT and urine 5-HIAA creatinine ratio of groups in Table I. The area of the rings is roughly proportional to the number of cases in the group; solid spots indicate single cases.

Platelet 5-HT before and after incubation in vitro with excess 5-HT was measured in 10 mentally defective subjects with serum 5-HT greater than 250 ng./ml. and in seven normal controls (Table IV). It will be seen that the raised serum 5-HT in the

<table>
<thead>
<tr>
<th>TABLE IV</th>
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<tbody>
<tr>
<td><strong>PLATELET, BLOOD, AND SERUM 5-HT IN MENTALLY DEFFECTIVE PATIENTS WITH SERUM 5-HT &gt; 250 ng./ml. AND IN NORMALS</strong>*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Platelet Count in 100,000/mm³</th>
<th>ng. H.T in 10⁶ Platelets</th>
<th>Saturation (2) as % of (3)</th>
<th>Blood 5-HT (ng./ml.) (1) × (2)</th>
<th>Serum 5-HT (ng./ml.) (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mentally defective patients</td>
<td>4-00 3-76 2-56 6-24 3-78 4-21 4-51 6-29 3-74 4-40</td>
<td>165 110 122 109 116 121 93 122 137 110</td>
<td>401 434 297 241 244 222 200 241 251 237</td>
<td>41 41 41 45 48 55 47 51 55 34</td>
<td>660 413 311 677 438 507 271 514 514 486</td>
</tr>
<tr>
<td>Mean ± S.E. (10)</td>
<td>4-35 ±0-38</td>
<td>121 286</td>
<td>42</td>
<td>479 368</td>
<td></td>
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<tr>
<td>Normal subjects</td>
<td>2-28 2-00 2-90 3-54 4-42 2-66 2-95</td>
<td>58 68 71 63 52 59 34</td>
<td>229 296 373 360 328 286 172</td>
<td>25 23 19 18 16 21 20</td>
<td>132 134 205 232 229 157 100</td>
</tr>
<tr>
<td>Mean ± S.E. (7)</td>
<td>2-99 ±0-40</td>
<td>58 292</td>
<td>20</td>
<td>168</td>
<td></td>
</tr>
</tbody>
</table>

*Blood and serum estimations were not always done at the same time.
with excess 5-HT, their mean content did not differ from that of normal platelets. From this it appears that the increase in platelet 5-HT is unlikely to be due to an increased affinity of the platelets for the amine. Their normal A.T.P. content is further evidence of this (Born, Ingram, and Stacey, 1958).

The origin of platelet 5-HT has not been definitely established. Platelets are unable to synthesize it and must therefore absorb it during their passage through organs which can. There is evidence that the concentration of 5-HT in the portal vein is higher than in the systemic circulation (Erspaner and Testini, 1959), and Adams (1960) has recently found an increase in serum 5-HT after the administration of drugs which increase intestinal motility. This suggests that part of the 5-HT in platelets is derived from the intestine but other organs may also contribute to platelet 5-HT and must be kept in mind. Brodie, Spector, Kuntzman, and Shore (1958) and Udenfriend and Weissbach (1958) have reported that the rate of turnover of 5-HT in the brain is many times that in the intestine.

Apart from our mentally defective patients a high serum 5-HT level is found in the carcinoid syndrome (Thorson, 1958) when it is due to a considerable increase in production by tumour tissue. It has also been reported in a single case of an obscure neurological disorder not associated with mental defect (Southren, Warner, Christoff, and Weiner, 1959) where there was no evidence of increased synthesis.

The increased 5-HIAA/creatinine ratio found in many of our cases of mental deficiency does suggest an increased 5-HT synthesis but this is based on the analysis of random specimens and on the assumption that creatinine excretion is normal. More detailed studies are needed before an increased 5-HIAA output can be accepted. If an augmented synthesis is the explanation of the high serum 5-HT found, a higher correlation would have been expected between urinary and serum findings. The low correlation obtained may reflect inevitable errors in a method of assessing 5-HIAA excretion without the collection of 24-hour specimens, and this would be in keeping with the much higher between-group correlation.

An increased 5-HT synthesis is not the only way in which platelet 5-HT might be raised and other possibilities merit consideration, although these are rendered less likely by the raised 5-HIAA excretion found. Depressed inactivating mechanisms can produce this result (Pletscher and Bernstein, 1958). Increased mean platelet life might lead to a similar change and the raised platelet count lends this possibility some support. A final possibility is that intracellular storage of 5-HT might be at fault and that, as a result, more 5-HT is available for absorption by platelets; but there is no evidence of this at present.

There is no apparent connexion between any of these explanations of a raised serum 5-HT level and mental deficiency. Nor have our attempts to correlate it with aetiological factors or clinical features proved very fruitful. In cerebral palsy a high serum 5-HT is associated with gross mental deficiency and this might be of value in the diagnosis of mental defect in spastic infants, for all the mentally normal cases we investigated had a normal serum 5-HT. Mongolism, now known to be a different type of genetic abnormality (Lejeune, Gauthier, and Turpin, 1959), was the only well-defined cause of mental deficiency in which the serum 5-HT was consistently normal. The single case of mongolism with a serum 5-HT above normal being a case with a severe anoxic incident at birth.

Anoxia is probably an important causative factor in the cerebral palsy symptom group (Bailey, 1958) although most of the direct evidence to this point is retrospective and therefore difficult to assess. However, Ranck and Windle (1959) have been able to produce an experimental condition in the rhesus monkey, with many features in common with cerebral palsy in man, by subjecting the animals to anoxia at birth.

In most cases of dementia we examined, the serum 5-HT was higher where there had been an anoxic episode. However, in many cases of mental deficiency with a high serum 5-HT there was no history of anoxia or of factors predisposing to it.

In this work it has not been possible to correlate biochemical abnormalities with histopathological changes nor have we investigated the metabolism of other biologically active amines. We hope to get some further information on both these points.

**Summary**

The serum 5-HT concentration and urine 5-HIAA/creatinine ratio in 83 mentally defective patients have been compared with those of 68 subjects in various control groups. In many of the defective cases both were raised. The results are analysed and discussed.

We are indebted to Dr. P. Armitage for discussion and advice, to those physicians who made their patients available for this investigation and especially to Dr. B. H. Kirman, Dr. B. W. Richards, Dr. A. Walk, and Dr. F. W. Bowyer for their helpful cooperation; to Miss Lilith Emslie, Mrs. Doreen Willis, and Mr. C. R. J. Ruthven for technical assistance, and to Roche Products who defrayed the salary of Mrs. Willis.
C. M. B. Pare, M. Sandler, and R. S. Stacey

References


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Relationships Between British and Russian Medicine and Neurology, and the Role of the National Hospital, Queen Square, London, in the Development of Russian Neuropathology. N. I. Grashchenkov.


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*J Neurol Neurosurg Psychiatry* 1960 23: 341-346
doi: 10.1136/jnnp.23.4.341

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