# ADRENOCHROME AS THE CAUSE OF SCHIZOPHRENIA: INVESTIGATION OF SOME DEDUCTIONS FROM THIS HYPOTHESIS

By

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## The Working Hypothesis

Osmond and Smythies (1952) have given reasons for reviving the view originally put forward by Bleuler (1950) that schizophrenia is essentially a disorder of metabolism, and have suggested that some substance chemically related to mescaline might be the causative agent. Hoffer, Osmond and Smythies (1954) have begun an investigation of this hypothesis and have found that adrenochrome, an oxidation product of adrenaline which is probably a normal intermediate metabolite, has active hallucinogenic properties. These authors do not regard adrenochrome as being unquestionably the toxic agent in schizophrenia, but suggest that it or some closely related substance, having the indole ring and derived from adrenaline, is involved. They also advance the opinion that the metabolic fault consists of an overproduction of adrenochrome or similar substances. Such a view necessarily implies either overproduction of adrenaline or a blocking of one or more of the paths of adrenaline detoxification in the body which do not lead through adrenochrome. As adrenaline is derived from tyrosine the hypothesis is essentially one of abnormal tyrosine metabolism. From this hypothesis certain deductions can be made.

## Deductions

A. *Abnormal pigmentation.* Tyrosine (which may be ingested as such or derived in the body from phenylalanine) is also a precursor of the normal biochrome melanin, one metabolic path leading through adrenaline and adrenochrome. It is to be expected that any interference with this chain of reactions will produce an abnormality of pigmentation (compare, for example, Addison's disease, phenylpyruvic oligophrenia, etc.). One such abnormality, increased formation of melanin and its deposition in the skin, has been described in schizophrenia (Loehner, 1938), and Hoskins (1946) is of the opinion that disorder of the adreno-sympathetic system, which is involved in pathological pigmentation, is one of the most constant features of this disease. Clearly the type of pigment anomaly, increase or decrease, will depend on the point of interference with the metabolic path. In phenylpyruvic oligophrenia the break occurs in the first stage, the conversion of phenylalanine to tyrosine, so that it is to be expected that shortage of pigment will be found, and this is well known to be the case. In the present disease the abnormality is assumed to consist of an excess, either by overproduction or accumulation, of adrenochrome. As adrenochrome is a very unstable substance and is oxidized to melanin at physiological pH without enzymatic aid, it is to be expected that an overproduction of melanin will result, and a preponderance of the dark type of individual be found in schizophrenics.

B. *Negative association with the allergic states.* It has been shown by Lucy (1954) that schizophrenics have a greatly increased tolerance to histamine.



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Adrenaline is one of the most satisfactory forms of treatment of the acute allergic states, i.e. acute histamine poisoning. In experimental anaphylaxis, i.e. acute histamine poisoning, one of the findings is melanuria (Haden and Orr, 1924), suggesting that excess adrenaline is being produced in an attempt to combat the effects of the histamine, and eventually proceeding to melanin *viâ* adrenochrome. It has been shown that concentrations of the order of $10^{-6}$ of adrenochrome have an antihistamine action (Hutcheon, 1955), so that the assumption that abnormally large amounts of adrenochrome are accumulating could explain this increased histamine tolerance in the schizophrenic subject. From this it follows that there should be a greatly reduced incidence of the allergic states in a population of schizophrenics.

C. *Ascorbic acid metabolism.* It has been shown that ascorbic acid prevents the oxidation of adrenaline to adrenalone, the immediate precursor of adrenochrome, in surviving slices of adrenal gland (Heard and Welch, 1935). It is well known that in certain cases of Addison's disease the pigmentation of the skin is much lessened by administration of large amounts of ascorbic acid. It has been shown, *in vitro*, that concentrations of sodium chloride below physiological limits accelerate the destruction of ascorbic acid and produce increased formation of melanin from both tyrosine and adrenaline (Lea, 1945). The occurrence of a schizoid state in Addisonian patients is well known. From these facts it seems that an attempt to treat schizophrenia with sodium chloride and ascorbic acid would be justifiable.

D. *Tyrosine metabolism.* Any attempt to treat schizophrenia by interfering with the amino-acid intake appears, at first, to be a highly speculative and possibly dangerous undertaking. However, Bickel, Gerrard and Hickmans (1953) described such remarkable clinical improvement in a case of phenylpyruvic oligophrenia following carefully controlled reduction of phenylalanine intake that experiments in treatment of schizophrenia along similar lines, i.e. reduction of tyrosine and phenylalanine intake to the physiological minimum, would seem to be justified.

E. *Abnormal substances in the urine of schizophrenics.* By analogy with the finding of melanuria in experimental anaphylaxis it might be expected that this or some similar urinary abnormality would occur in schizophrenics. Churchman (1924) reported five instances of melanuria in cases of unspecified mental disease. No further reference to this work has been found in the literature, but it does seem probable that some abnormal indole body, or excess of the normal indole derivatives, might be present in the urine of schizophrenics.

It has been found possible to investigate two of these deductions, viz. abnormal pigmentation and negative association with allergic states.

## Material and Methods

A series of 1,008 cases of schizophrenia occurring in men serving in the forces during the recent war has been investigated. The cases used were not entirely free from selection as (1) they were limited to the male sex, (2) they were of the standard of physical and mental fitness necessary for service in the forces, (3) they were limited to the age groups of serving men, and (4) they were diagnosed during the years 1943–44. This last restriction was imposed in order that ample time should have elapsed since the first diagnosis to allow of its full confirmation. It must be pointed out that factors (1), (2) and (3) above prevent direct comparison between this series and those drawn from the general population.

The eye and hair colours of these men were recorded by recruiting boards, together with the age at the date of the observations. Such records cannot have a great degree of accuracy, but reasons have been given (Lea, 1955) for regarding them as adequate for the present purpose. These colours have been compared with those of a control series of 5,127 cases of injury, previously prepared for such a purpose (Lea, 1952) and subjected to the selection factors (1), (2) and (3) as in the schizophrenic series. Eye colours have been recorded as blue or non-blue, hair colours as fair or dark. In addition the data have been classified according to the scheme devised by MacConaill (1941–42), viz. blond=blue eyes and fair hair, dark=dark eyes and dark hair, glaucope=blue eyes and dark hair, cyanope=dark eyes and fair hair. For the purposes of this investigation blue, grey-blue and grey eyes have been grouped together as blue, all others as non-blue. Fair, blond, light brown and flaxen hair have been grouped as fair, all other colours including red as not-fair (=dark).

For the investigation of the allergic states the full case histories, including hospital and other records since discharge from the forces, of a random series of 500 of these schizophrenics were searched for evidence of any form of allergy. This was also done in a control series of 500 cases of head injury. Head injuries were chosen for the control series because the case notes in this type of injury went more fully into details of past history, family history, etc., because of the possibility of post-traumatic personality changes, than did those of other types of injury. Even so it is very probable that the incidence of allergy in these head injury cases as recorded here was an understatement, for their case histories as a whole were not as detailed as those of the schizophrenics. It must also be noted that the incidence of the allergic states in these cases gave no indication of the true incidence of these conditions in the general male population of the same age groups. This was because two important selective factors operated, (1) men with obvious allergy would not be accepted for the forces, and (2) those with severe allergic conditions which became manifest after enlistment would be discharged for this reason. The incidence here was of the mild allergic conditions, overshadowed in immediate importance by either the head injury or the mental condition. It is to be noted that these selective factors apply to both the schizophrenic and head injury series and therefore cannot be regarded as having affected the findings of this investigation.

## Results

The eye and hair colours and the MacConaill types of 1,008 cases of schizophrenia, together with those of 5,127 cases of injury, are given in Table I. It will be seen that the percentages for all ages differed very little in the two series, and the values of $chi^2$ for comparison of eyes, hair and MacConaill types were 0·300, 2·557 and 4·199, giving values for P of 0·5–0·7, 0·1–0·2 and 0·2–0·3, all non-significant results. However, it is known that the proportions of these different colour types vary with age, so the data were subdivided into the age groups 15–19, 20–24 and 25 years and over (further division was not possible because of the smallness of the numbers in the higher age groups). Comparison again produced no significant findings in eye colour, $chi^2=4·223$, P=0·1–0·2, but in hair colour and the MacConaill types some striking differences were found. For hair colour $chi^2=12·702$ which, with 3 degrees of freedom, gave P less than 0·01, and in the MacConaill types $chi^2=18·381$ which, with 9 degrees of freedom, gave P between 0·02 and 0·05. In hair colour the age group 15–19 years contributed 10·582 to the total of $chi^2$,

TABLE I

*The Eye and Hair Colours of 1,008 Schizophrenics and 5,127 Cases of Injury, in 5-Year Age Groups*

(Figures in brackets are percentages, "age" refers to age at which data were recorded)

| Character | Age Groups 15–19 Schizophrenics | 15–19 Injury | 20–24 Schizophrenics | 20–24 Injury | 25 and Over Schizophrenics | 25 and Over Injury | All Ages Schizophrenics | All Ages Injury |
|---|---|---|---|---|---|---|---|---|
| Blue eyes .. .. | 169 | 907 | 279 | 1,099 | 159 | 1,034 | 607 | 3,040 |
| | (56·5) | (60·8) | (61·6) | (58·9) | (62·1) | (58·4) | (60·2) | (59·3) |
| Non-blue eyes .. | 130 | 585 | 174 | 766 | 97 | 736 | 401 | 2,087 |
| Fair hair .. .. | 58 | 426 | 112 | 420 | 48 | 383 | 218 | 1,229 |
| | (19·4) | (28·6) | (24·7) | (22·5) | (18·8) | (21·6) | (21·6) | (24·0) |
| Dark hair .. | 241 | 1,066 | 341 | 1,445 | 208 | 1,387 | 790 | 3,898 |
| Blond .. .. | 48 | 338 | 91 | 347 | 42 | 292 | 181 | 977 |
| | (16·2) | (22·7) | (20·1) | (18·6) | (16·4) | (16·5) | (18·0) | (19·1) |
| Dark .. .. | 120 | 497 | 153 | 693 | 91 | 645 | 364 | 1,835 |
| Glaucope .. .. | 121 | 569 | 188 | 752 | 117 | 742 | 426 | 2,063 |
| Cyanope .. .. | 10 | 88 | 21 | 73 | 6 | 91 | 37 | 252 |
| Totals in age groups | 299 | 1,492 | 453 | 1,865 | 256 | 1,770 | 1,008 | 5,127 |

this group alone having a value for P of much less than 0·01, and in the MacConaill types the same age group contributed 11·731 to the total of $chi^2$ with a value for P of less than 0·01. In each case the remaining two age groups had non-significant values for P of 0·1–0·2 and 0·05–0·1 respectively.

It is also known that the proportions of the colour types vary in different parts of Great Britain. The data were further subdivided into areas of birthplace, but of these only the London area had figures sufficiently large for statistical comparison. The data for this area are given in Table II. For hair colour in the

TABLE II

*The Eye and Hair Colours of 246 Schizophrenics and 1,054 Cases of Injury Born in the London Area, by Age Groups*

(Figures in brackets are percentages, "age" refers to age at which data were recorded)

| Character | Age Groups 15–19 Schizophrenics | 15–19 Injury | 20–24 Schizophrenics | 20–24 Injury | 25 and Over Schizophrenics | 25 and Over Injury | All Ages Schizophrenics | All Ages Injury |
|---|---|---|---|---|---|---|---|---|
| Blue eyes .. .. | 40 | 170 | 58 | 192 | 48 | 220 | 146 | 582 |
| | (56·3) | (59·0) | (57·4) | (52·9) | (64·9) | (54·6) | (59·3) | (55·2) |
| Non-blue eyes .. | 31 | 118 | 43 | 171 | 26 | 183 | 100 | 472 |
| Fair hair .. .. | 12 | 103 | 29 | 97 | 13 | 97 | 54 | 297 |
| | (16·9) | (35·8) | (28·7) | (26·7) | (17·6) | (24·1) | (22·0) | (28·2) |
| Dark hair .. | 59 | 185 | 72 | 266 | 61 | 306 | 192 | 757 |
| Blond .. .. | 10 | 80 | 24 | 79 | 13 | 67 | 47 | 226 |
| | (14·1) | (27·8) | (23·8) | (21·8) | (17·6) | (16·6) | (19·1) | (21·4) |
| Dark .. .. | 29 | 95 | 38 | 153 | 26 | 153 | 93 | 401 |
| Glaucope .. .. | 30 | 90 | 34 | 113 | 35 | 153 | 99 | 356 |
| Cyanope .. .. | 2 | 23 | 5 | 18 | 0 | 30 | 7 | 71 |
| Totals in age groups | 71 | 288 | 101 | 363 | 74 | 403 | 246 | 1,054 |

London area, by age groups, $chi^2=10·916$, P being between 0·01 and 0·02. The age group 15–19 years contributed 9·239 to the total, P for this group being much less than 0·01. Eye colour gave $chi^2=3·483$ with a value for P between 0·3 and 0·5. There were too few in the cyanope group of the MacConaill types for comparison to be made.

The incidence of various allergic states in 500 cases of schizophrenia and 500 cases of head injury is given in Table III. (Eczema was only included when

TABLE III

*The Incidence of Allergic Conditions in 500 Cases of Schizophrenia and 500 Cases of Head Injury*

| Allergy | Schizophrenia No. of Cases | Head Injury No. of Cases |
|---|---|---|
| Asthma | 1 | 4 |
| Urticaria | 0 | 2 |
| Eczema | 0 | 7 |
| Henoch's purpura | 0 | 1 |
| Hay fever, rhinitis | 0 | 4 |
| Drug sensitivity | 0 | 4 |
| All types | 1 | 22 |

there was a history of recurrent attacks since childhood and the diagnosis confirmed by a dermatologist.) Difficulties arose as there were no firm grounds for ranking different types of allergy as equal from the point of view of the seriousness of the disease. It could not be held that they represented equal degrees of hypersensitivity, or equal degrees of histamine poisoning, etc. It was also impossible to grade the various types of allergy on the basis of their risk to life, for though it would be generally held that, as an example, asthma is a more serious condition than drug sensitivity, yet the majority of asthmatics have a normal length of life, whereas one of the cases of head injury in the present series had such a near-fatal reaction (severe urticaria, oedema of the glottis, etc., necessitating emergency treatment) to the routine service inoculations that he was provided with a letter of warning to anyone who might have to treat him in the future. It was finally decided that for the present purposes all the various allergic states would have to be ranked equal as cases of undue histamine sensitivity, without regard to the degree of such sensitivity, and the data treated as individuals with allergy as opposed to those without, and the calculations made on that basis.

A further problem was provided by the cases of drug sensitivity. These were confined to the head injury series and consisted of abnormal reactions to penicillin and other antibiotics. The difficulty was due to the fact that all the open head injury cases received sulphonamides, penicillin, etc., as routine treatment, whereas the schizophrenics did not, though many of the latter did have treatment with antibiotics for various reasons. Clearly the risk was not the same in the two series, and it was decided that the cases of drug sensitivity should be omitted from the calculations, though they are shown in Table III for the sake of completeness.

Family history of allergy was also recorded. It was found that in only one schizophrenic, the solitary case with asthma, was there a family history of allergy as compared with seven in the head injury series. These cases were unfortunately too few for statistical treatment. Finally one case of head injury had both asthma and eczema, reducing the number of affected men in this series to 17.

Comparison of the 17 cases of allergy in the head injury series with the one case in the schizophrenic series, using Yate's correction, gave $chi^2=13\cdot230$ which, with one degree of freedom, gave a value for P of less than $0\cdot001$.

## SUMMARY OF RESULTS

(1) The analysis of the data showed that there was a highly significant excess of dark hair in schizophrenics in the age group 15–19 years, with no significant difference in eye colour, as compared with a series of cases of injury. The deficiency of blonds is probably significant but cannot be said to be definitely so.

(2) There was a highly significant deficiency of individuals with allergic conditions in the schizophrenia series.

(3) For both the excess of dark hair and the deficiency of allergy in the schizophrenics the probability of the observed results being due to chance is approximately 1 in 1,000.

## Discussion

*The excess of dark haired subjects.* (The very important fact that this excess is limited to one age group is discussed later.) There are at least four possible explanations of this excess.

(1) Schizophrenia has a hereditary basis, and the metabolic abnormality concerned is present from birth. As a result excess melanin is formed from the beginning, and the subjects show an undue proportion of the dark haired type. This implies that in schizophrenics with fair hair the disease must have some cause other than adrenochrome intoxication.

(2) Schizophrenia has a hereditary basis, the gene responsible being on the same chromosome as that for dark hair. This does not attribute the dark hair to the metabolic abnormality responsible for schizophrenia, but only implies linkage between the two genes and therefore provides an explanation of the fact that all schizophrenics do not have this hair colour.

(3) It might be supposed that as the excess of dark hair is statistically significant there should be a significant deficiency of blonds. (It must be remembered that the definition of blond is blue eyes and fair hair.) This is not necessarily the case. Eye colour in man is generally regarded as being fixed within a few months of birth, but it has been shown by Riddell (1942) that there is a change with advancing age, the pattern of the iris becoming more complex with a general appearance of deepening of colour. This change, however, requires special examination to demonstrate it, and it has not been possible to show it within the age limits of the present series. On the other hand the darkening of hair with age is marked (Steggerda, 1941), and is well shown in the control series. Therefore the excess of dark hair in schizophrenics does not necessarily mean that the subjects have been dark from birth. Their eye colours do not now differ from those of the control series, possibly their hair colours did not do so at birth, and the excess of dark hair now found would be due, not to a hereditary factor but to increased melanin formation from the excess of adrenochrome. It is to be noted that the symptoms of schizophrenia appeared one to three years after the recording of the eye and hair colours. This implies that (*a*) the excess of adrenochrome has not been present from birth, but (*b*) it was present for some time (years) before the development of obvious schizophrenic symptoms. This possibility again provides no explanation of schizophrenia in blonds, other than a different cause.

(4) The fourth alternative arises from a consideration of evidence from previous work on schizophrenia and other subjects.

(*a*) Bellak (1947) has summarized the evidence from investigations of liver function in schizophrenics. Although there is still disagreement on hippuric acid excretion, there is a body of facts providing firm evidence of impairment of liver function in this disease. Of particular interest here is the description by Hoffer, Osmond and Smythies (1954) of an unpleasant experience of a volunteer for experimental adrenochrome psychosis, which was attributed to the results of a previous attack of infective hepatitis, and has caused these authors to issue a warning against such experiments in persons with a history of liver disease.

(*b*) There is no firm evidence of an over-production of adrenaline in schizophrenics, and in fact what evidence there is suggests that there may well be a deficiency. Conclusions may also be drawn from the negative evidence provided by cases of tumour of the adrenal medulla. The twenty-three papers on this tumour quoted by Ackerman and Regato (1947) have been searched, and in no case has there been found any description of symptoms which could be regarded as schizoid in character. It follows that over-production of adrenaline *per se* is not an adequate explanation of the hypothesis that adrenochrome is the cause of schizophrenia, as in these cases of medullary tumour there is a gross excess of adrenaline but no evidence or even suggestion of any abnormality in the subsequent metabolism of this substance. It then becomes necessary to assume an accumulation of adrenochrome in the schizophrenic subject because of blocking of one or more of the paths of adrenaline detoxification. These paths are (Bacq, 1949):

1. Excretion unchanged in the urine.
2. Storage within cells.
3. Deamination and subsequent oxidation of the side chain.
4. Esterification of the phenolic hydroxyl groups.
5. Oxidation through adrenochrome to melanin.

There are no grounds for assuming that (1) and (2) are affected, and the activity of (5) is the basic hypothesis under investigation. There remain (3) and (4), both of which probably take place in the liver. It follows that a damaged liver could result in diversion of unusual amounts of adrenaline to path (5), with a necessarily higher than normal concentration of adrenochrome in the body.

(*c*) It has been shown (Lea, 1953) that there is a highly significant excess of the dark type of individual in cases of trophopathic hepatitis. (*Trophopathic* hepatitis is defined as necrosis of the liver due to deprivation of some substance essential to the life of the cells, in contrast to *toxipathic* hepatitis which is necrosis due to the direct action of some toxin, whether chemical or bacterial (Himsworth, 1947). It was suggested that this association was due to a hereditary metabolic abnormality linked with colour rather than to two different effects of one gene. There was no evidence of such an association in cases of toxipathic hepatitis.

The fourth explanation may now be formed as follows: it is suggested that in persons with a hereditary liver defect, or in those who have suffered damage to the liver as a result of toxipathic hepatitis, the metabolic path leading through adrenochrome to melanin would carry more adrenaline than is usual. As a result the concentration of adrenochrome in the body would rise, with the production of the symptoms constituting schizophrenia. The preponderance of the dark type of individual in this disease would then be due to the known association with trophopathic hepatitis; the presence of the blond type would be attributed to liver damage resulting from toxipathic hepatitis in this pigmentary type. In other words, schizophrenia would be yet another example of a state that may be produced by either hereditary or environmental factors, the end results of the two causes being indistinguishable.

It was noted that many of the cases of schizophrenia used in this investigation had infective hepatitis within two years of the onset of mental symptoms, and it was at first thought that this might provide confirmation or otherwise of the above suggestion. However, it soon became clear that the population under investigation had been exposed to an abnormal risk of contracting infective hepatitis, due to the fact that so many of them had served in areas in

which epidemics of the disease had occurred, so that any results obtained would necessarily be biassed and valueless.

*The limitation of the excess of dark haired subjects to the age group 15–19 years.*

Two obvious explanations present themselves:

(1) That included in the syndrome known as schizophrenia are at least two distinct conditions, (*a*) one due to intoxication by adrenochrome or some related substance with an average age of onset of less than 20 years, and (*b*) the other due to some other cause or causes with an average age of onset of at least 30 years.

(2) That schizophrenia is a single disease, due to adrenochrome or similar intoxication, but with two modes of origin, (*a*) hereditary factors with an average age of onset of less than 20 years, and (*b*) environmental factors, e.g. liver disease, which may operate to produce schizophrenia at any age.

Unfortunately, schizophrenia is so extremely varied in its manifestations that it might very well consist of a number of different diseases. The position is so confused that it must be stated, on the one hand, there is no proof whatever that schizophrenia is a single disease, nor, on the other, is there any proof that it does contain a number of different entities. Certain pointers appeared in the course of the present investigation, one of them being the presence of two maxima in the age incidence at about 20 and 30 years, another that whereas the group with the earlier onset tended to undergo steady deterioration with eventual death in an institution from intercurrent infection, the group with later onset suffered little intellectual impairment, did not remain in institutions, and not infrequently died by suicide. However, investigation of both these trends failed. On the age distribution, it is clear that service personnel are strictly limited to certain age groups, and that the average of 20 years is too high because of the absence of age groups below 17, and that 30 is too low because of the absence or rarity of the groups over 50. It must also be remembered that the frequencies in the age groups which are represented in the services are not distributed as they are in the general population, and it is quite possible that if they were truly representative the two observed maxima would merge into one. On the question of the course and end of the disease it became evident that the younger age groups were still far too young for any firm statements to be made about their progress. Whether these apparent trends are anything more than the results of selection can only be determined by a long-term investigation of unselected material from the general population.

*The negative association with allergy.* There is little to add on this point except to emphasize that the deduction made from the adrenochrome hypothesis was fully confirmed by the evidence. However, consideration of Lucy's work on histamine tolerance, on which this deduction was based, showed that a further approach to the question of the homogeneity or otherwise of schizophrenia could be made. Lucy gave data from 50 cases of schizophrenia, dealing with them from the point of view of whether the histamine tolerance became less with the duration of the disease, and found that there was no evidence of such a lessening. From this he concluded that even after 25 or more years the disease was still the same. But these data can also be regarded from the point of view of whether or not the abnormal histamine tolerance is associated with the age at onset of the disease. Clearly if this increased tolerance were associated with only the younger age groups this would provide evidence for the view that schizophrenia contains more than one disease. The data were rearranged for this purpose and the correlation between the age at onset and the maximum

amount of histamine tolerated was examined. The correlation coefficient between these two factors was found to be −0·03, a value which does not even approach a significant level, The evidence from Lucy's work therefore lends no support to the view that schizophrenia is a syndrome containing more than one disease.

## Conclusions

Using the view that schizophrenia is due to intoxication by adrenochrome as a working hypothesis certain conclusions can be drawn from this investigation.

The two deductions, that a population of schizophrenics should show an increased incidence of dark pigmentation and a decreased incidence of the allergies, have been confirmed. These results support the hypothesis of adrenochrome intoxication but the limitation of the excess of dark hair to the age group 15–19 years requires further explanation. Of the explanations suggested it is considered that the evidence is most consistent with the hypothesis that the metabolic fault is due to hepatic insufficiency, and that this may be due to either hereditary or environmental factors. This explains the preponderance of dark types in the age group 15–19 years (hereditary), the presence of other pigmentary types at all ages (environmental), the evidence of liver damage in schizophrenics, the persistence of abnormal histamine tolerance throughout the course of the disease and the absence of a correlation between age at onset and degree of histamine tolerance. It is also consistent with the view, supported by re-examination of Lucy's data, that schizophrenia is a single disease. No suggestion is made that this hypothesis of liver dysfunction as the cause of the excess of adrenochrome has been established, nor does it seem possible to investigate it further with the material on which this paper is based. The hypothesis is put forward as one which offers an explanation of the observed data, but at the same time only too clearly emphasizes that many, possibly most, of the facts of schizophrenia are still unknown. It will be noted that the grounds on which the presence of an excess of dark types was originally deduced have now been discarded in favour of the hypothesis of liver dysfunction.

## Summary

(1) Accepting the views of Hoffer, Osmond and Smythies, that adrenochrome or some related substance is the cause of schizophrenia, as a working hypothesis, the deductions were made that a population of schizophrenics should contain an excess of deeply pigmented types and a deficiency of persons with allergy.

(2) 1,008 cases of schizophrenia and two control series, one of 5,127 cases of all types of injury, the other of 500 cases of head injury, have been investigated. It was found that there was a highly significant excess of dark hair in the schizophrenics, limited to the age group 15–19 years, and that there was a highly significant deficiency of allergic conditions.

(3) Explanations of these findings have been discussed, and the suggestion made that the evidence is most consistent with the view that the excess of adrenochrome is due to hepatic dysfunction, both hereditary and acquired.

(4) Re-examination of Lucy's data on histamine tolerance in schizophrenics supports the view that schizophrenia is a single disease.

(5) Other deductions have been made from the working hypothesis, but they cannot be investigated on the material available. Their investigation would help to establish, or disprove, the adrenochrome hypothesis.

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