SCHIZOPHRENIA AND THE PINEAL GLAND*

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Introduction

Von Bertalanffy said, "For defining a so-called disease entity a triad of criteria is necessary: a specific etiology, a specific syndrome of symptoms and a specific course. In the light of the criteria mentioned, apparently schizophrenia does not qualify as a disease entity. Its etiology is unknown; its symptomatology offers a large spectrum of alterations from the normal; and no specific course or therapy is known." (5)

If we accept the basic concept that schizophrenia is the clinical manifestation of different pathologies, searching for a unified biochemical explanation for every type of schizophrenia would be illogical. Scientists working on this problem have published many interesting and encouraging papers. Others attempting to replicate previous findings have become discouraged upon obtaining inconsistent results.

Today we realize that schizophrenia is not an entity and thus might be due to differing pathologies together with differing biochemical abnormalities, but unfortunately as yet there are no methods which provide biochemical differentiation. We are still at the data-collecting stage in the biochemistry of schizophrenia. Every schizophrenic patient has to be observed closely wherever this is possible and the result of the biochemical investigations recorded. During this period, if some unusual results are recorded and observed repeatedly they should be investigated. Eventually these observances will tend to divide schizophrenics into various subgroups. The clinical syndrome now known as schizophrenia will most likely separate into a number of different diseases in much the same way as the 'jaundice' of eighteenth century medicine became a variety of diseases.

We were lucky enough to recognize the so-called eye-skin syndrome (26) and we further investigated this observation. Our findings stimulated us to continue research. Diffuse melanosis was found both in treated and in untreated schizophrenic patients (27); the significance of this diffuse pigment deposit had been investigated but no final explanation found. We explored the formation of the pigment and analyzed its biophysical role (28). As yet our results do not give the key to the classification of schizophrenia. However, they are encouraging and offer a logical working hypothesis in some areas of the schizophrenic process.

A. Eye — Skin Syndrome

Between 1959 and 1963 a number of patients at Riverview Hospital, Essondale, B.C. who had been receiving large doses of chlorpromazine developed a peculiar pigmentation of exposed skin areas. This pigmentation was very marked in twenty-one patients and less so in another forty-nine. Of the twenty-one markedly affected patients, twelve were noted to have grossly visible corneal and lens opacities. All these patients were female Caucasians, 80 per cent of whom were amenorrheic from the onset of their mental illness. Their ages ranged from 25 to 62 years, the average age being 43. All the affected patients had been receiving chlorpromazine (Cpz.) for a minimum of three years prior to the onset of the skin discolouration; their doses averaged from 500 mg. to 1500 mg. daily. Most of these patients were also receiving other tranquillizers (26).

SKIN MANIFESTATIONS. Pigmentation of the skin was found only on exposed areas and was most marked on the face, appearing in a 'butterfly' distribution. Other noticeably marked areas included the extensor surface of the arms, the forearms, the hands and the back of the legs. In many cases it was visible in the nailbeds, though it was not evident on the palms nor was it ever found in the mucous membranes. In a

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three-year period some ten thousand patients were examined; of these, seventy showed some discolouration — an occurrence rate of less than 1 per cent. On the face the discolouration varied from a mild diffuse violaceous colour on the cheeks and on the nose, to a deep purplish-grey, metallic colour over the entire face. This discolouration often became apparent first in the summer but did not disappear during the winter months, nor did it fade significantly during the first six months after discontinuing drug treatment. No associated blistering of the skin was noted nor were any texture changes discovered.

Skin biopsies were done on several of the patients showing skin discolouration, samples being taken from both pigmented and non-pigmented areas. Further biopsies were then done on patients who were on prolonged high doses of Cpz. but had so far shown no discolouration.

In the affected skin areas the most pronounced microscopic finding was the presence of a marked accumulation of golden-brown, fine, granular pigment in the macrophages situated around the capillaries in the superficial layers of the dermis. The epidermis itself seemed unremarkable except for an occasional suggestion of absence of the normal melanin in the basal layers of the epidermis. The melanocytes in the skin were DOPA positive. No inflammatory reaction was noted. In the affected patients, biopsies from clinically unaffected sites were similar to those just described but not to the same degree. The histochemistry of the pigment will be described in detail later.

After our observations were published we became aware that there were already two papers published dealing with facial discolouration in patients treated with phenothiazine. In 1957, Saunders (61) observed a female patient who developed a dermatitis while on Cpz. and upon histologic examination increased melanin-like pigment was revealed. However, Saunders did not specify whether the pigment was in the epidermis or in the dermis. In 1962 Perrot and Bourjala (52) reported that some patients on phenothiazine medication had developed a metallic bluish discolouration on the face — *visage mauve* and *teinte cuivrée*. They hypothesized that this was a toxic reaction; pigment was never mentioned and no follow-up was made.

Immediately after our publication, Zelickson and Zeller (74) reported their observation regarding the skin manifestations of Cpz. treated patients. They studied the affected areas with electron microscopy (75) and found dense osmiophilic granules in the skin of patients presenting with this syndrome. However, these were in no way similar to melanin granules. Zelickson concluded in 1965 that these granules were not pure melanin themselves nor wholly deposits of the drug but a combination of the two.

In 1964 Perry *et al.* (53) studied the skin of one of our patients; they extracted the Cpz. metabolites and analyzed the extracted material, and suggested that this was 7-hydroxychlorpromazine or a metabolite of this compound and that this material was deposited in the pigmented skin in addition to melanin or pseudomelanin.

Besides the above mentioned papers several other reports have been published showing similar results and the general consensus has been that discolouration is the result of a melanin or melanin-like substance in the dermal area (2, 3, 4, 10, 12, 19, 33, 35, 43, 60).

The pathological changes occurring in the skin have been shown by biopsy to consist of clumps of pigment with the staining characteristics of melanin clustered around the blood vessels in the dermis. Electron-microscopical reports are conflicting. One author (34) found typical appearances of melanin in the skin with some additional osmiophilic particles in the endothelial cells of the blood vessels in the dermis, while another author (76) found no natural melanin in the dermis.

OCULAR MANIFESTATIONS. In twelve of the severely pigmented twenty-one cases there was a peculiar hazy-brown pigmentation of the exposed sclera and cornea as well as a small central lens opacity. On ophthalmoscopic examination the

lens opacity appeared as a dark brown, irregular stellate opacity with a dense central area and radiating branches. No fundal changes were found. Pigmentation was seen also in the bulbar conjunctiva in the palpebral fissure. Slit lamp examination revealed the corneal lesion to be stromal in situation and to consist of yellowish-white granules mainly in the posterior half of the cornea but less densely concentrated in the peripheral cornea than in the centre. The lens opacity consisted of yellow-white dots concentrated at the centre and having radiating arms situated in the anterior subcapsular pole (26). Following our publication containing information on ocular changes, interest in this manifestation increased rapidly. Many papers followed from the United States, England, Australia and France (11, 16, 17, 18, 47, 48, 64, 69). All these observations were identical with ours but they gave more detail regarding the pigment deposit and tried to correlate the dose of phenothiazine with the appearance of ocular manifestations.

The general opinion nowadays is that in the eye the lens, the cornea and the conjunctiva are usually affected but the retina rarely shows any change. The first changes usually occur in the lens. The early lens and corneal changes may be visible only with the slit lamp; later they can be seen with an ophthalmoscope or even with the unaided eye. Whilst no fundal changes were found in most of the surveys carried out, a few cases have been reported with clustering of pigment at the periphery of the retina. In most surveys no visual defects were found. The frequency of eye changes varies from 30 per cent to 70 per cent in different surveys.

The ocular changes seem to be clearly related to the amount of drug given and also to the daily dose. Some investigators believe that side effects are not common if the daily dose is small. At first it was supposed that only Cpz. could induce these eye changes until Edler (18) reported similar eye pathology in five of seventy-four patients who had never had this drug but were on other phenothiazines.

The eye-skin syndrome was observed in schizophrenic patients who had been treated with Cpz. for a prolonged period of time and who had been on fairly high dosages. However, the discolouration in the faces, hands and feet of schizophrenics was observed and described long before phenothiazines were in use. In 1912 Cornell (15) considered a cyanotic, metallic bluish discolouration of exposed skin areas in dementia praecox to be pathognomonic of this illness. Bleuler (6) described the same in 1920. MacKenzie Shattock (63) in 1950 described similar pigmentation in female schizophrenics but this pigmentation had never been observed in male psychotics. In Shattock's very detailed analysis of his cases pigmentation of the mucous membranes was never seen and there was a strict correlation between the patients' psychotic condition and the pigmentation. The eye manifestations had not been observed before chlorpromazine was used.

Changing the medication or discontinuing the phenothiazine therapy does not seem to affect the eye manifestations. However, with the skin discolouration it is different; this changes only if the patient is off the medication for at least two years or if his condition improves. We checked up on three patients, all of whom were medium dark, who had escaped from our hospital and were out for more than two years, and on their return their colour was practically normal (29).

It seems to us that the pathogenesis of eye and skin manifestations is not quite identical. The eye changes are very likely due to the drug; they correlate with the dose and they had also never been observed before Cpz. therapy started. Our long-term observations showed that corneal opacities might improve considerably, although over a period of seven years we never saw much change in the lenticular deposits (stellate shaped opacities). Prien and Cole (55) observed similar eye changes in schizophrenic patients regardless of whether they were on high or low doses of chlorpromazine, on a placebo or on treatment with some other material. However, they found an eye change of 35 per cent in the high-dose group;

in the low-dose group a change of 12 per cent was noted whilst those on a placebo showed an 8 per cent change; and in the routine treatment group only 5 per cent of the patients showed any change. At nine months after conclusion of their study approximately 50 per cent of the corneal opacities had improved greatly or disappeared completely. The eye deposit might be due to direct light effect polymerizing Cpz. metabolites in the cornea and in the lens. The skin discolouration is only partially induced by the medication; it was observed before this therapy was started and it is reversible. The patient's illness or the seriousness of his illness might have a role in its genesis. This aspect of these manifestations seems logical to us in the light of our working hypothesis which will be described later.

McDonald *et al.* (44, 45) administered large doses of Cpz. (40 mg./day) to albino, red and black guinea pigs in an attempt to reproduce the abnormal oculocutaneous pigmentation reported in the human subject. After giving the drug for a period of twelve months and exposing the shaved animals continuously to ultraviolet light, no dermal deposits of pigment were shown. Following the drug treatment slit lamp examination of the guinea pigs' eyes revealed lens opacities in all the animals. Lens opacities had been consistently identified earlier in the female guinea pigs. These interesting experimental findings supported our hypothesis that the eye and skin manifestations are not identical in their genesis.

B. Diffuse Melanosis

Having observed melanin-like pigment in the eye and in certain areas of the dermis of schizophrenic patients on Cpz. therapy we resolved to follow these patients closely. During this period five of these patients died unexpectedly. We assumed that there might be pigment deposits in their internal organs similar to those shown in their skin and eyes. A detailed autopsy and histological examination were done on these patients. Melanin-like pigment was present throughout the reticulo-endothelial system, in the parenchymal cells of the internal organs, in the endocrine organs, the heart, the lungs and in the perivascular spaces of the brain (13, 30). The sudden death of these patients drew our attention to similar cases where death was sudden and unexpected although no facial discolouration had been present. Re-examination of autopsy tissues from seven of the latter cases histologically revealed similar pigment deposits in identical areas.

These two groups of patients had similar pigment deposits in their eyes and internal organs; they had been diagnosed as schizophrenics and all of them had been on chlorpromazine for a long time. It was natural for us to try to correlate generalized melanosis with phenothiazine therapy or with the schizophrenia process or with both. To check this aspect necropsy material was re-examined from between the years 1947-49 when phenothiazines had not been in use. Autopsy material from some fifty schizophrenics was re-examined and the previously described pigment was found in the same distribution but in lesser amounts. Necropsy material from some twenty-five non-schizophrenic patients was also examined and similar pigment was found in very small amounts. In most cases the difference between the schizophrenic and non-schizophrenic was prominent. Our conclusion was that in some forms of schizophrenia there is abnormal pigment production, causing the pigment to be deposited in the eyes, the skin and the internal organs, and this abnormal pigment formation is further intensified by the phenothiazine medication.

With all these observations the following questions were raised:

a) What is the nature of this pigment?
b) Where is it produced?
c) How does it affect the bodily function?
d) If it affects the bodily function should it be prevented?
e) Is it related to some form of schizophrenia?

WHAT IS THE NATURE OF THIS PIGMENT? Histochemically the pigment is a golden brown colour and has a

fine granular appearance when stained by hematoxylineosin. It proved to be DOPA positive in the skin and DOPA negative in the internal organs tested (liver, lung, kidney, brain). It does not stain for iron by Gomori's method, nor for bile by Stein's iodine method, nor for lipid by Sudan IV. It does not polarize light and does not fluoresce in the wave length for phenothiazine. Fontana's method of staining for melanin is positive and it could always be bleached by H_2O_2 in less than twelve hours. With Nile blue sulfate it stains dark green, and with Nile blue sulfate followed by acetone extraction it remains dark green. With acid-fast stain it is negative.

As can be seen the pigment we found in many schizophrenics had all the histochemical characteristics of melanin. Although none of these methods was specific for melanin we accepted these deposits as melanin until otherwise proven.

The possibility of the pigment being a phenothiazine metabolite was considered. The fact that necropsy material from 1947-49 also contained this pigment showed that most of it could not be a phenothiazine metabolite although part of it might be. If this was so it must be a polymerization molecule having the same histochemical characteristics as melanin.

To analyze the pigment further, pigment-containing tissues were investigated by electron spin resonance (ESR) and examined by electron microscopy (28).

It has been known since 1954 that natural and synthetic melanin have an ESR signal which has been attributed to trapped free radicals in the pigment (7, 14, 24, 73). Skin, liver and thyroid tissues were examined by us in a liquid nitrogen temperature. An E3 Varien ESR spectrometer was used. The signals — width and shape — were identical with the signal of synthetic melanin and of frog skin melanin. We concluded that we were dealing with signals the origin of which was very likely melanin.

Skin, liver and thyroid biopsy material taken from treated, dark patients and from non-treated, normal-coloured patients was examined by electron microscopy. All the materials examined contained fairly high amounts of electron-dense bodies which were thought to be melanin (36, 62).

Although it is known that there is no special test for melanin, results from these different experiments show evidence that the dark pigment is likely to be melanin. By definition melanin is a non-chemical term describing the black or brownish pigment of biological origin, which has been considered to be a nitrogen-containing polymer (7). Melanins have also been defined as natural pigments occurring in living organisms at all levels of evolution (49, 50). So melanin is a macro-molecule which is built up (as far as we know from the research of Nicolaus and his group) from eleven or twelve molecules (adrenochrome might be present if adrenaline is transformed to melanin). These building blocks of melanin are ubiquitous in the living body, so that melanin can be produced in practically every organ and cell. Even some phenothiazine metabolites can be transformed to indolquinones and polymerization of phenothiazine metabolites is real, but according to the definition, melanin is a non-chemical term and all macro-molecules which have certain physical and chemical characteristics are called melanin regardless of the original monomers from which they were formed.

WHERE IS IT PRODUCED? Melanocytes in skin biopsies taken from schizophrenic patients on phenothiazines show a high rate of activity and the DOPA reaction is strongly positive. The skin window method shows a large number of cells with melanin in their cytoplasm. From these findings it was assumed that in schizophrenic patients on phenothiazine, melanin was produced in the melanocytes of the epidermis at a higher than normal rate. Furthermore, the pigment was deposited in the dermis and picked up by the macrophages and the monocytes and carried away by the bloodstream and deposited in the reticuloendothelial system and in the parenchyma of the internal organs (68). In order to recheck this

assumption the blood of twenty schizophrenics was tested with the buffy coat technique, and to our surprise we were unable to find any pigment-containing cells in eighteen patients, whilst in the two remaining cases there was only one visible pigment-containing cell in each. All cases checked had been diagnosed as schizophrenics, they had a bluish discolouration of the face and they had been on high doses of chlorpromazine for a lengthy period. In every case the buffy coat of blood was used and at least ten slides were examined. These slides were stained with the Wright-Giemsa method. From these findings the idea that melanin could be produced in high amounts in the skin and transported into the internal organs seemed unlikely. The possibility of melanin formation *in situ* in different organs was entertained and some observations showed that this assumption might be possible. Firstly, there is no correlation between the discolouration of the skin and the pigment deposit in the liver or thyroid. We examined biopsied liver and thyroid tissues from normal-coloured patients and their organs contained large amounts of pigment. Secondly, with histochemical methods the skin and meningeal slides stained identically with the melanoma which was used as a control. However, the internal organs, liver, lung and thyroid were different, especially when the Fontana method and bleaching were used. It is well known that in vitiligo there is no melanin in the skin whilst the brain melanin is intact (21, 22). The melanin in the skin is tyrosine melanin but that in the brain is supposed to be catecholamine melanin (20). If this is correct the pigment found in our patients' internal organs could differ in its origins — the building blocks of melanin are ubiquitious.

HOW DOES IT AFFECT THE BODILY FUNCTION? The large amount of pigment deposit in the functional cells of practically every organ raised the question of how it affected the function of the cell. In 1963 Helmy and Hack (37) histochemically and metabolically investigated the structure and function of the liver of the amphibian, *Amphiuma* Means. The liver of this amphibian contains dark pigment which has been thought to be melanin. At this time it was known that melanin can undergo reversible oxidation-reduction, and it is a strong electron acceptor and donor. This investigation showed that the *Amphiuma* liver contained melano-protein. These granules are believed to act as a self-contained oxidation-reduction system. Various histochemical techniques demonstrated an exceedingly low level of mitochondrial activity in *Amphiuma* liver. Lastly, the glycogen from the liver was very slowly depleted by fasting, epinephrine and glucagon — a contrast with the case of glycogen depletion in the rat. Helmy and Hack's conclusion suggested that there was a fundamental difference between the metabolism of pigment-containing *Amphiuma* liver and the pigmentless rat liver. These observations stimulated us to investigate further the thyroid and the liver function of pigmented and non-pigmented patients, since these two organs are usually heavily loaded with pigment granules in schizophrenics. For thyroid function the tyrosine loading test was used (59) and for the liver function the glucagon-induced hyperglycemia test was used.

The oral tyrosine tolerance test has been described in detail by many investigators; we used the method published by Rivlin *et al.* (59). L-tyrosine powder (Grade 1) 50 mg/Kg. was given orally to the patient in the morning and the blood samples were taken prior to the amino acid and then every half hour for three hours. Tyrosine was analyzed by a fluorometric method. Forty treated chronic schizophrenic patients were tested with the following results:

fasting level:	11.53 ± 5.68 mg/ml	(mean ± 2 S. D.)
30 min. level:	13.44 ± 9.65 mg/ml	(mean ± 2 S. D.)
peak value:	31.65 ± 25.49 mg/ml	(mean ± 2 S. D.)

Siersback-Nielsen (65) investigated extensively the value of this test in normals, hyperthyroids and hypothyroids and tried to correlate the fasting values and the peak

values after an oral tyrosine loading dose. Malamos *et al.* (41) investigated the fasting level of serum tyrosine in different thyroid pathologies. Our results were approximately the same as those reported in the aforementioned papers. However, Rivlin *et al.* measured the fasting values and plasma tyrosine concentration 30 minutes after tyrosine loading and until the peak value was reached. According to these results our patients' values are in the hypothyroid range. This is very interesting because schizophrenics have always been suspected of being in a mild hypothyroid state. Unfortunately, the published results are controversial and more investigation is needed.

Glucagon test: 1 mg. of glucagon was given intravenously in fasting states during a period of three to five minutes. The blood sugar was determined before glucagon was given and also at 30, 60, 90, and 120 minutes after its administration (70). The Folin-Wu method was used for blood sugar determination. In normals the rise is 60 ± 30 mg. per cent over the fasting level. Our results:

mean fasting level (99%):
93.07 ± 24 mg.%
mean maximum level (99%):
128.00 ± 41 mg.%
mean rise (99%):
34.95 ± 36 mg.%

These results are not conclusive; the mean rise value appeared to be mainly at the low level for the accepted normal. No conclusion can be made without more investigation.

Parallel with these investigations the concentration power of the kidney was also tested in the same patients and in patients who showed advanced skin pigmentation. Our observation showed that as the kidney tubules are the areas which contain the highest amount of pigment, their concentration power would be limited first. In most cases the concentration power was narrowed and this could be correlated with the length of illness of the patients. We included no patients who had ever shown signs of kidney disease.

IF IT AFFECTS BODILY FUNCTION SHOULD IT BE PREVENTED? The frequency of the eye (about 30 per cent) and of the skin manifestations (less than 1 per cent) and the diffuse melanosis observed in schizophrenic patients surprised everybody working in this field. The general feeling was that pigmentation was detrimental to the patient's appearance; that it might cause visual impairment; and that the functions of the internal organs could be impaired by such deposits of pigment. The general opinion was that abnormal pigment production should be prevented. Our first cases had all been on Cpz. therapy. This drug was blamed for the pigmentation and the medication was changed or, in cases where it was possible, it was discontinued. All patients were observed closely and for the next six months no changes were noticed in their condition. We should mention here that the most pigmented patients were the most psychotic ones; consequently it was very difficult to control their condition with small doses of phenothiazines, and in some cases it was impossible. Treatment was needed and it was therefore necessary to find other means of prevention rather than just changing their medication.

Our assumption was, and still is, that most of the pigment is melanin. Potts proved that the drug deposit was pigment-dependent, and drug metabolites could be found only where pigment was *a priori* present. It seemed logical to interfere with the pigment production and try to block it. The basic idea was that if pigment formation could be blocked efficiently the pigment already present would be excreted and little or no new pigment would be produced and deposited in the skin, the eyes and the internal organs. Following this, since the drug deposit is pigment-dependent, less drug would be deposited in the above named organs.

The classical concept of melanin synthesis is that of Raper (57) and Mason (42). Their concept of melanin biosynthesis involves a series of stepwise oxidations and reductions leading to 5, 6-indolquinone, which was assumed to undergo condensation and form the polymer. This process starts from tyro-

sine, and the presence of oxygen and tyrosinase is needed, tyrosinase being a copper enzyme. During 1962 Nicolaus and his group published their studies of melanin biosynthesis. They cited evidence that as many as ten different substituted indolquinones could be involved as monomers. Furthermore, Blois (7) recently proposed that melanin biosynthesis probably involves free radical polymerization, producing a highly random three-dimensional polymer in which the number of possible structures is very large. Blois concluded that there are probably no two molecules of melanin exactly alike. Nicolaus (50) classified biosynthesized melanins in two large groups — tyrosine melanins which are enzyme-dependent and catechol melanins, with respect to insolubility, chemical inertness, infrared absorption and having an electron spin resonance. Blois concluded that this molecule is a member of the class of random irregular polymers, as are the melanins.

The production line of melanin is controlled by two groups of factors — the so-called darkening and lightening factors (40). The darkening factors are alpha and beta melanocyte-stimulating hormones (MSH), androgens, estrogens and thyroid extracts. Lightening factors are epinephrine, norepinephrine, serotonin and melatonin. Pigment will be over-produced when there is an absolute or relative dominance of darkening factors. As to the relative strength of these factors the following should be noted: if we mark androgen as one unit, the estrogen hormone and the thyroid hormone will be the same or less and the alpha and beta MSH would be one thousand or more. Similarly, the strength in the group of lightening factors would be: epinephrine marked as one unit, norephinephrine and serotonin would be one unit each or less and melatonin would be one thousand or more.

From the above outlined physiology of the biosynthesis of melanin, the possibilities for a blockage of pigment synthesis are as follows (31).

i) *To decrease the needed material for melanin synthesis.* From the tyrosine, oxygen and tyrosinase, the simplest way is to interfere in the tyrosinase function by decreasing the copper intake or increasing the copper output or using both methods. We used d-penicillamine as a copper chelating agent. With this method we expected to decrease the enzyme-dependent melanin production.

ii) *To decrease the photo-produced melanin.* The photo-produced melanin production is not affected by the method used in i), but it is supposed to be light-dependent and therefore putting the patients in a dark room theoretically has to influence the light dependent melanin formation. This process acts in two ways — directly by electron donation in free radical polymerization and indirectly through the pineal gland by influencing the melatonin cycle. We used this method in only a few cases.

iii) *To increase the concentration of the lightening factors.* More melanin is produced than normal if there is an absolute or relative increase in darkening factors. At this moment we have no knowledge or means to decrease effectively the most effective darkening factors, alpha and beta MSH, and therefore we tried to increase the lightening factors by giving melatonin injections. Once again only a few cases were treated in this way.

i) Six middle-aged white female patients were chosen for the first trial, all of whom had a mild to a dark metallic bluish discolouration on the face. Four of them had not been on Cpz. for periods ranging from three to six months yet showed no change in their colour, whilst the two remaining patients were still on this drug. For this trial we used a copper-chelating agent, d-penicillamine, giving doses of 300 mg. three times daily for six days a week. On the seventh day we substituted a mineral supplement; this mineral supplement was designed to replace all the minerals which were lost with the use of penicillamine, with the exception of copper. The diet was a general diet containing approximately 100 g. of proteins, 250 g. of carbohydrates with the remainder fat, making a total in-

take of 2,100 to 2,500 calories. During this four-week course of treatment the urinary copper excretion was measured in five of these patients. Measurements had of course been made prior to the commencement of the course and during it.

At the end of the four weeks the colour of four patients was markedly improved, one showed moderate improvement and one was unchanged. By marked improvement is meant that there was a nearly complete disappearance of the bluish colour, leaving a residual healthy brown tan on the face. Moderate improvement resulted in conversion of the blue metallic colour of the cheeks to a healthy brown tan, but on the nose and frontal area the metallic blue colour persisted. The four markedly improved patients were not on Cpz., whilst the other two patients were on 1,200 mg. daily throughout the trial period (31).

ii) Two middle-aged female patients were put in a dark room for four weeks. Their colour was a deep metallic blue shade and neither of them was on Cpz. Their diet was exactly the same as that mentioned above. The room was illuminated by a dim red light. One patient showed marked improvement with complete disappearance of her metallic blue colour and the other improved only slightly. Subsequently the second patient was put on d-penicillamine and her bluish colour disappeared (31).

iii) In July and August 1966, we tried giving 10 mg. of melatonin daily to six patients. The injection was given at 10 a.m. and the diet followed was the same as that previously mentioned. This trial lasted six weeks but showed no immediate convincing results (32).

Follow-up observations of 36 blue patients.

Thirty-six patients who had been dark or medium blue in 1964 and who had been treated with different psychopharmacologicals were re-examined in 1967 (29). Three patients were still blue and two of these were continuing to receive Cpz., but the third patient had not received this drug since 1963. The total dose of Cpz. given to these three since 1960 was 2,700 g., 1,500 g., and 1,000 g. respectively.

Fourteen patients are now lightly coloured and showing no bluish tint whatsoever. Four of them, the darkest ones, had been treated with d-penicillamine. The other ten did not receive treatment for melanosis. Eight of these ten are still on doses of 600-1,000 mg. Cpz. daily; the remaining two have had none since 1965.

A further fourteen patients in this group have normal colouring. Six had been treated with penicillamine. The last eight had not had any treatment for their melanosis; (seven had had no Cpz. since 1967 and one is still on this drug).

Of the remaining patients in this group two were discharged and showing normal colouring after d-penicillamine therapy. They are now on 400 mg. of Cpz. daily. The last three patients in the group died of megacolon and pulmonary edema (29).

Our experiences from the previously described methods and from the follow-up of our thirty-six patients show that a high dose of Cpz. for a prolonged period of time will be likely to induce the eye-skin syndrome and cause melanosis, though not necessarily always. We still have patients on fairly high doses of this drug whose colour is normal. Our conclusion at this moment is that this drug in high doses is one factor in the induction of the melanosis but the presence of other factors seems likely. Other workers got the same impression (67).

Our main purpose in the above trials was to treat or reverse the eye-skin syndrome and to block the abnormal melanin production which was supposed to be a damaging side effect of phenothiazine therapy. From these experiments we found that abnormal melanin production and pigmentation could be successfully reversed by putting the patient in a negative copper balance. A second method of reversing the melanosis might be achieved by putting patients in the dark, since darkness very likely stimulates melatonin formation. Melatonin in amphibians is a strong lightening factor and this lightening affect of melatonin has been used successfully on vertebrates, for example,

dogs (58). On humans the physiologic effect is still under investigation.

While treating bluish-coloured patients, an interesting observation was made by our co-working psychiatrists. Their impression was that patients whose colour improved also improved psychiatrically. This impression was shared by several other people and it was therefore decided to check this aspect.

SCHIZOPHRENIA AND COPPER METABOLISM?

This series of experiments was completed in several stages. Firstly, a chelating agent and a normal diet were used, then secondly, a chelating agent and a low copper diet were given in a metabolic unit, and thirdly a chelating agent and a low copper diet were tried in a normal ward set-up.

i) D-penicillamine and general diet. Twenty-four chronic schizophrenic male patients with ages ranging from 36 to 54 years were chosen. Their previous medication was left unchanged. However, for four weeks half of these men were put on d-penicillamine (3 x 300 mg/day) and the other half were given a placebo. The results were not conclusive and showed little significant change in the condition of any of the patients.

ii) D-penicillamine and low copper diet in a metabolic unit (51). Ten chronic schizophrenic male patients were chosen, with ages ranging from 23 to 42 years. All were on a diet of low copper intake with less than 1.5 mg. of copper daily. Five patients were treated with a dose of 1,200 mg. of d-penicillamine daily and five were given a placebo. This course lasted for six weeks. The urinary copper excretion was checked before the trial and then three times during the trial period. Serum ceruloplasmin levels were determined during the same period and these were well within the normal range and did not change during the investigation.

The results were assessed by histology from skin biopsies, by the increase of urinary copper excretion, by psychological tests and by psychiatric assessment. In patients treated with d-penicillamine and low copper diet the formation of melanin in the skin was inhibited; the urinary copper excretion was significantly increased; there was also a remarkable improvement in the symptoms of schizophrenia in these patients.

iii) A trial with d-penicillamine and a low copper diet was conducted in a normal psychiatric ward. Thirty female chronic schizophrenics were chosen, with ages from 35 to 50. A daily diet of less than 1.5 mg. of copper and 1,200 mg. d-penicillamine was given. This was carried out for a period of four weeks. The results were not successful since most of the patients ate, in addition to their low copper diet, regular food from other patients. The copper intake could not therefore be controlled and psychiatric improvement was not noticeable.

All these trials were designed as pilot projects. Even so it seemed to us that some conclusions could be drawn from the results. Penicillamine side effects were never seen. The bluish colouration could be changed with a copper-chelating agent alone, although a combination of a chelating agent and a low copper diet is more effective. Psychiatric improvement could be seen in some of the schizophrenics when in a negative copper balance. The colour change once reversed appeared to last for years, even when the patient went back on Cpz.

C. Chlorpromazine — Melanosis — Schizophrenia

Since the introduction of Cpz. in 1953 it has become one of the most prominent and widely used drugs in psychiatry. Its therapeutic success stimulated intensive research for additional psychopharmaceuticals. Within psychiatric hospitals an attitude of pessimism and despair toward mental illness was replaced by one of hopefulness and confidence, and mental hospitals were transformed into active treatment centres. Many hospitals discarded the closed ward system in favour of an open-door policy. However, psychopharmaceuticals are potent drugs and world literature contains many reports on their harmful side effects, involving the

cardiovascular, endocrine, secretory, dermatologic, renal, hematologic and central nervous systems. Millions of patients around the world have been treated with these drugs. This vast experience testifies that serious complications are very rare indeed and psychiatrists are now learning how to minimize the risks of pharmacotherapy. Good medical practice requires balancing risk against the good which can be achieved, and the good far outweighs the risk as far as the phenothiazine group is concerned.

After fifteen years in clinical use and discussion in more than 10,000 publications we might ask what we know about the metabolism and biological effect of the chlorpromazine molecule. This line has been extensively investigated by Forrest (23, 25) and by many others in the last few years. Cpz. *in vivo* might be metabolized by ring oxidation forming free radical intermediates and by side-chain change. Piette (54) postulated that the free radical intermediates, having extreme stability, are responsible for the psychotropic activity. Blois (8) showed that intraperitoneally administered S35 labeled Cpz. can be localized in tissues containing melanin. He theorized that there was some form of binding between this drug and some constituent unique to these pigmented tissues; it was later assumed to be the pigment itself. Bolt and Forrest (9) further investigated this binding and concluded that it is a charge-transfer reaction, Cpz. being the donor and melanin the acceptor. Wollemann and Laborit (71) found that injected Cpz. *in vivo* increases the glucose-6-phosphate dehydrogenase activity in liver and brain, and they concluded that the reason for this effect is that the drug acts as an electron donor.

Szent-Gyorgyi (38) and his co-workers investigated the Cpz. molecule from a physico-chemical point of view. They found its characteristics exciting because of its unique biological activity. It is the first substance found which has an anti-bonding, highest-filled orbital in its normal stable state. Therefore it can be expected to be an exceedingly good electron donor, capable of forming stable charge transfer complexes. Riboflavine has similar values but it is unstable and auto-oxidizes rapidly. Pullman (56) achieved the same results from quantum-mechanical calculations on the electronic structure of phenothiazines.

Szent-Gyorgyi (66) after these fascinating findings concluded: "These ideas may become the starting point of various trains of thought . . . if the symptoms of schizophrenia can be influenced by electron donation, then, perhaps, a lack of electrons may be involved in the genesis of this disease, and if so the question comes up: what has induced it? If the disturbance can be corrected to some extent by electron donation, could it now have been caused by the presence of an electron acceptor?" I think we have found the answer to Szent-Gyorgyi's question. Melanin is a very strong electron acceptor and is in fact an electron trap mechanism. If this is correct the melanin might induce a lack of electrons and, similar to several other electron acceptors — hyperbilirubinemia in newborns — inhibit oxidative phosphorylation and so damage the brain function. Cpz. as a strong electron donor fills up the spaces of lacking electrons; firstly, in the melanin molecules thereby increasing their amount; secondy, in the functional molecules of the cells, improving the previously malfunctioning oxidative phosphorylation (the proper energy production).

The electron transport system is very important in cellular energy production, (high energy phosphate bond formation). The electrons drop from a higher energy level to a lower one, cascading downward and releasing energy. This energy is immediately picked up by ADP and a high energy phosphate bond is produced in the form of ATP; this is one form of cellular energy storage. In the presence of an abnormal electron acceptor such as an electron trap mechanism, this energy flow would be affected and very likely fewer high energy phosphate bonds formed. The crucial factor in this malfunctioning energy production is the abnormal electron acceptor which in our case is the melanin molecule.

Normally melanin is present in the human body in the skin, the eyes, the meninges and in the basal nuclei in the brain. In many of our schizophrenic patients we found abnormally large deposits of melanin-like pigment in the internal organs. The question now is: is this abnormal pigment formation due to the presence of an abnormal increase in the material which is needed in pigment production, or is it due to a failure of the control mechanism?

As has already been mentioned, melanin is a giant molecule polymerized from 10 or 11 building blocks. These monomers are ubiquitous, appearing in every cell. Therefore every cell has the ability to polymerize the monomers into a melanin-like giant molecule. Knowing this we might suppose the real problem is in the control mechanism which keeps these monomers in balance or keeps the electron flow, that is, the energy production in balance. Unfortunately this control mechanism is hardly known in humans. In amphibians it is known that the darkening and lightening factors keep the mechanism in balance. But if we put the effective factors of these two groups in proper perspective, taking into account the fact that we are dealing with schizophrenic patients, the lightening factors would seem very important. Catecholamines and serotonin are the subject of many theories on schizophrenia; the melatonin is produced from serotonin and one of the enzymes needed in this transformation is a special methyltransferase. This transmethylating enzyme is present only in the pineal gland. Therefore it is very vulnerable since it might be metabolically inhibited or congenitally defective. If so, melatonin will not be produced or will be produced only partially and instead of melatonin, harmala alkaloid might be manufactured (46). In this case melanin production will not be controlled and so might be overproduced in the body and harmala alkaloids will be formed in the pineal gland. These alkaloids are hallucinogenic and therefore if the methyltransferase in the pineal gland is defective the patient might have diffuse melanosis and might also have hallucinations. Most of our patients showed this clinical picture.

Conclusion

There are many ifs in our theory, but starting from the fact that in many schizophrenics there is abnormal pigment produced and deposited in nearly every organ, it offers a logical working hypothesis. The pineal gland would be the locus of defect and its function will be our prime target for further investigation. This is not new; in fact, the history of research of the pineal gland is a very long one. Herophilos of Alexandria (325-280 B.C.) first mentioned the pineal body function as controlling the 'stream of thoughts'. The same idea was expressed in Descartes' (1596-1650) essays, when he claimed the epiphysis to be the seat of the soul. After the times of Descartes, interest in the mammalian pineal gland dwindled and it got the reputation of being a rudimentary organ of no great consequence until the existence of the endocrine organs was realized. At the beginning of this century Marburg was first to propagate the theory that the mammalian epiphysis would have an endocrine function related to the development of the sexual organs. In 1954 Kitay and Altschule (39) summarized the whole literature relating to the pineal gland. From the anti-serotonin effect of reserpine Woolley (72) assumed that the pineal gland has some role in the causation of certain schizophrenias. Pineal extracts have long been used in the therapy of mental illness, especially in schizophrenia, but with varied results (1). Our work is now centered around the lacking enzyme and the presence of harmala alkaloids.

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Each departed friend is a magnet that attracts us to the next world.

Jean Paul Richter
1763-1826