POST-MORTEM EXAMINATION.

There was practically no mesenteric or other abdominal fat. The spleen was enlarged, bright red, and the substance soft and diffluent. The heart and lungs were healthy. The stomach was slightly dilated and the mucous membrane was thin and pale. The mucous membrane of the small intestine was thin and appeared to be atrophied, and there were a few injected patches, but no ulceration. The mucous membrane of the large intestine appeared to be thin and glistening, otherwise normal.

No naked-eye abnormality was found in the endocrine glands, nor in the central nervous system. The pancreas, thyroid, supra-renal and pituitary were examined microscopically. No changes were found which could not quite well be accounted for by the terminal septicæmia. The first two segments of the cervical cord were examined, and in all sections stained by the Weigert-Pal method a considerable amount of marginal and pseudo-systematized demyelinization was found (see figure).

Sections of the skin showed very extensive surface keratinization, underlying which there were acute recent inflammatory changes with much polynuclear exudation and multiple thromboses in the smaller vessels.

The small bowel showed marked thinning of its walls, but a detailed examination of the mucous membrane was impossible owing to *post-mortem* desquamation. An impression was gained that this atrophy affected its lymphoid elements. (In subsequent investigation on another case this impression proved to be correct.)

A Case of Pellagra with Recurring Attacks.

By W. J. T. KIMBER, M.R.C.S., L.R.C.P., D.P.M., Medical Superintendent, Hill End Mental Hospital, St. Albans.

THE progress of a case of pellagra under observation for a period of five years, during which time many exacerbations of the pellagrous symptoms were noted, should be of considerable interest.

The ætiology of this condition remains obscure in spite of painstaking efforts by various observers on different lines, and, while a certain amount of hypothesis has been advanced, there is lacking that knowledge which should enable us to eliminate the spurious and co-ordinate the remainder into an intelligible and comprehensive whole.

A brief survey of the main theories as to causation will serve as an introduction to a study of the case-report.

Deficiency in biological value of protein.—According to this theory, the condition is due, not to an absolute deficiency of protein in the diet, which may in fact be present in quantities greater than are necessary to maintain normal health, but to a deficiency of those proteins which contain certain specific side-chains in their molecular composition, particularly tryptophane. This is present in a comparatively large amount in the protein of meat, eggs, peas, beans, etc., and, on addition of these to the diet, early cases of pellagra rapidly improve. Maize protein, consisting largely of zein, is deficient in tryptophane; hence the origin of the now generally abandoned maize theory. In this connection it must be remembered that it is only the amount of protein absorbed that can be

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taken into account, and that any conditions which lead to impaired absorption (and these are common in pellagra) reduce the amount of available protein.

Infection.—In America, in 1916 (1), attempts were made to establish the infective nature of the disease condition, and 16 persons for several months were fed on, or inoculated with, the epidermal scales and various bodily secretions of pellagrins, but without the disease being conveyed to them, and belief in the infective nature of the disease was discredited. Infection arising from the gastro-intestinal tract may yet prove to be an important factor.

Diarrhœa is an invariable, though not necessarily a persistent symptom of the condition; characteristic tongue changes are the rule; a deficiency of gastric hydrochloric acid is common, and the increased liability to infection and toxic absorption under these circumstances is generally appreciated.

Recently attempts have been made, particularly by Dr. Susman at Manchester, to demonstrate the presence of an organism in the blood, and this has been successfully done by him in a number of cases, including the subject of the present report.

Endocrine deficiency.—Changes in the histological appearance of the endocrine glands, particularly the thyroid, are very commonly, if not invariably, found, and it has been pointed out by Dr. G. A. Watson (2) that the condition occurs in many cases, and is in some way connected with the degenerative changes found in these glands, at the climacteric, and in cases of dementia præcox.

The similarity of many of the manifestations of this condition to Addison's disease, *e.g.*, pigmentation, asthenia, etc., long ago led to the adrenal glands being suspect, and some clinicians have claimed benefit from the administration of adrenalin, but, while degenerative changes in the adrenal glands are usual, the evidence points to these being a stage in the progress of the disease rather than a causative factor.

McCarrison (3) concluded that there was an attempted exercise of an emergency function in the adrenal glands in states of inanition and avitaminosis due to deficiency of vitamins A and B in the diet. The importance of the observation in this connection will be seen later.

Toxic effects.—Degenerative changes and widespread fibrosis amongst the organs suggest a toxæmia, but whether this arises from an organismal infection, or is due purely to metabolic or endocrine disturbance, is not clear. Dr. Susman (4) believes that the toxic material is excreted by the kidneys because peritubular degeneration and subsequent fibrosis are observed. The central neuritis, which appears to be a constant feature, must also be considered a result of toxæmia.

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Vitamin deficiency.—In view of recent work on vitamins by Prof. Plimmer (5), it would appear that the possibility of vitamin deficiency playing a part in the production of pellagra must be reconsidered. He has shown that not only a certain minimal amount of vitamin B is necessary to maintain health on a given diet, but that if the diet is increased by the addition of other foods, without increasing the previously adequate amount of vitamin B, deficiency symptoms will result. In other words:

$$\frac{\text{Vitamin B supply}}{\text{Total food}} = \text{a constant.}$$

The changes observed by Prof. Plimmer in chickens with a partial deficiency of vitamin B, and by McCarrison (6) in pigeons completely deprived of it, were intestinal stasis with retention of putrid food residues and absorption of toxic products of putrefaction, the subsequent polyneuritis being attributed to this toxic absorption. Fatty infiltration of the intestines was seen in the case of the chickens on a partially deficient diet. The similarity of these intestinal conditions to those seen in pellagra is striking.

Again, pellagra amongst the Turkish prisoners of war in Egypt was markedly diminished when the protein diet was increased, and this was attributed to the high biological value of the proteins used, chiefly beans and lentils, but it is just these proteins also which are rich in vitamin B.

The following figures are taken from the Report of the South Carolina Pellagra Commission of 1912:

1·37% of those taking milk daily developed pellagra.
4·88% ,, ,, fresh meat daily developed pellagra.
1·37% ,, ,, no meat at all developed pellagra.

Daily administration of milk and eggs was insufficient to afford protection. Such figures do not support the contention that deficiency in the biological value of the protein consumed is always an essential factor.

It has been pointed out by Seale Harris (7) that the Great War was, in effect, a repetition of Goldberger's Rankin Farm Experiment of 1914 (8) on a large scale. He observes that with the extremely poor and unbalanced diets of France, Belgium, Germany, Austria-Hungary and England no increase in pellagra was recorded, and in Italy, where the disease was a scourge before the war, there was a great decrease in its incidence, while other diseases associated with nutritional deficiencies, *e.g.*, tuberculosis and scurvy, were rife during the war period.

A similar observation as regards pellagra was made both by

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Dr. Watson (9), at Rainhill, and by the author at Hill End (10), but at the time no explanation for it was apparent.

In this connection it should be noted that while the war-time diet was defective in some directions, more especially as regards protein, it contained a higher percentage of vitamin B than many diets normally consumed.

REPORT OF CASE.

K. B—, female, æt. 30. Admitted March 29, 1921; died November 3, 1926.
Diagnosis.—Primary dementia; pellagra. *Causative factors:* None ascertained.
Family history.—No evidence of mental or neurotic disorder was elicited.
Previous history.—Severe periodic headaches began in 1916; some mental instability noticed for five years previous to admission. Recently violent and resistive.
State on admission.—Mentally inaccessible and appears oblivious of her surroundings. Restless at times, tearing at or twisting up her clothing. Gives no reply to questions. Habits defective and troublesome with food. Physical condition moderate. Dental caries, but no other signs of gross disease. Urine contained a trace of sugar, but no albumen or acetone.

Progress.

April 4, 1921: Troublesome with food—hand-fed.
May 30: Very resistive; still requires hand-feeding.
June 25: Slight diarrhœa, with a little blood and mucus.
August 26: Slight diarrhœa for four days.
September 21: Pellagra. Thickened and pigmented skin on back of hands, with bracelets. Impetiginous eruption on face and forehead. Much thinner. Tongue clean. Depressed and restless.
December 29: Dull, idle, seldom talks. No signs of pellagra.
1922 and 1923: Unstable mentally and liable to periods of mild excitement. Looking after herself as a rule, but not doing other work. No evidence of pellagra noted.
March 29, 1924: Pellagrous dermatitis reappearing. Diet increased by one egg and one pint of milk.
December 30: Pellagrous dermatitis, which has persisted in a slight degree, is disappearing.
March 28, 1925: Skin condition shows no pellagrous changes.
August 23: Well-marked pellagrous appearance of both hands with complete bracelets. Tongue clean but not characteristic. No diarrhœa, but bowels rather loose. Reflexes appear normal.
September 29: Rash disappearing. She is at times troublesome with food for a few weeks and then eats well.
August 8, 1926: Thickening and darkening of skin on hands with partial bracelets. Tongue red and denuded. Central nervous system appears normal.
August 16: Diarrhœa. Restless and noisy.
September 10: Quieter, taking food well: rash almost disappeared.
October 15: Well-marked pellagrous dermatitis both hands, with some areas infected and purulent. Septic left heel. Diarrhœa, but no mucus; tongue has aphthous patches. Knee-jerks, wrist and biceps jerks brisk, but not markedly exaggerated. Mentally dull, resistive, defective in habits, but cognizant of her surroundings.
October 18: Taking food better. On yeast 1 drachm *t.d.s.*
November 2: Getting weaker, with slight but persistent diarrhœa. Gangrenous slough on left heel. She has had twitching of face for the last two days.
November 3: Since yesterday morning has had choreiform spasms of upper limbs, more marked in the evening. At 7.40 a.m. she was seized with convulsions of face and upper limbs lasting about ten minutes, at the end of which time she collapsed suddenly, and died at 7.50 a.m.

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Post-Mortem Examination.

Certified cause of death: Pellagra.

External appearances.—Body thin, small sacral bed-sores. Ulcer of left heel with gangrenous patch. A few old pigmented scars on body and limbs. Symmetrical pigmented areas on dorsum of both hands extending obliquely across the fingers and upwards to wrists, extending a few inches over the lower anterior surface of the fore-arm.

Head.—Dura thick and adherent to skull, especially over right fronto-parietal region. Pia-arachnoid normal in appearance. No congestion. Brain 48 oz. Some flattening of cerebral convolutions over right fronto-parietal region, but no general wasting. On section, distinction between white and grey matter was well marked. Ventricles not distended; ependyma appeared normal. Cord showed no gross changes.

Thorax.—Passive œdema both lungs. No tubercle found. Heart muscle thin and substance friable. No dilatation; no valvular disease. Periostitis was present on pleural surfaces of ribs from about 1½ in. from vertebral joint outwards on 4th to 9th left and 4th to 8th right ribs.

Abdomen.—Stomach: Walls thin, mucosa thin and rugæ very few. Areas of injection, but no ulceration seen. Small intestines: Very thin and atrophic throughout. Valvulæ conniventes were present in upper part of intestine, but were absent from the greater part. Areas of injection were seen in places, but no ulceration. Some specially atrophic areas were noted.

Cæcum: Areas of congestion more marked than elsewhere. Large intestine: Walls thin, mucosa atrophic without rugæ, but no ulceration. The mucosa was a light greyish colour for the greater part. Areas of congestion present. Liver: (51 oz.): Congested plum-coloured appearance. Spleen (2¾ oz.): Soft. Kidneys (right 3¾ oz., left 4¼ oz.): No gross changes. Capsules stripped easily. Ovaries: Hard and deeply crenated. Thyroid: Soft and pale.

Histological Findings.

Thyroid.—Vesicles largely obliterated by proliferation and give appearance of large masses of rounded or cuboidal cells. On close examination vesicular boundaries are still discernible, although in large areas even these vesicular boundaries are lost, and the cells are in large consolidated masses divided only by fibrous tissue. Very few vesicles are of the usual size and only occasionally do these contain colloid.

Pancreas.—Congested, especially noticeable in a large number of the islets. There has probably been some hæmorrhage. A fair number of islets are considerably enlarged.

Ovary.—Cystic; considerably fibrosed; numerous hyaline bodies. An appreciable amount of functioning tissue left.

Liver.—Portal tracts prominent; liver-cells atrophic; some small fibrous nodules.

Spleen.—Probably some hyperplasia.

Kidney.—Glomeruli of a firm appearance suggesting some excess of fibrous stroma. There is also peri-tubular necrosis well established about the larger tubules.

Stomach.—Mucous membrane atrophic.

Ileum.—Pigment of old hæmorrhage in submucosa.

Colon.—Mucous membrane atrophic.

Heart-muscle.—Atrophy—some fatty degeneration.

Nervous system.—Various parts of the cerebrum, medulla and upper cord were examined and showed changes associated with chronic mental disease, *e.g.*, those usually found in long-standing cases of dementia præcox. There was some chronic thickening of vessels and non-fibril-forming glia proliferation, but no evidence of recent inflammatory reaction.

The question of central neuritis could not be definitely settled, as, owing to the tissues having been inadvertently placed in a chrome fixing fluid for a time, staining by the aniline dyes was unsatisfactory.

The "Betz" cells examined were "ghost-like," as were also some of the larger pyramids, and where a nucleus was visible it was eccentric. The "ghost-like" appearance did not appear to have been due to faulty staining, as other nerve-cells stained fairly well. It seems almost certain that central neuritis was present.

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I am indebted to Dr. G. A. Wilson, of Rainhill, for the reports on the histological appearances of the nervous system, and to Dr. W. Susman, of Manchester University, for similar reports on the other organs.

Final Comments.

An interpretation of the pathological findings is not easy. There are changes in the gastro-intestinal tract, in various endocrine glands, in the central nervous system, and in addition an organism was isolated from the blood during life.

Two main questions arise: (1) How far are the changes due to pellagra as distinct from those present in many cases of chronic mental disease, especially dementia præcox? (2) In what sequence do the pathological changes attributable to pellagra occur?

It must be admitted that at present no definite answer can be given to either of these questions, but it is legitimate to advance a theory, remembering always that further observations may disprove, modify or confirm it.

The earliest symptoms in this, as in the majority of cases, were refusal of food, and diarrhœa. Clinically, therefore, there are some grounds for thinking that the oldest lesions are those of the gastro-intestinal tract. On the other hand, alterations in reflexes, as is also usual, were late in appearance, and such are often not very definite, although evidence of central neuritis can usually be obtained histologically. This leaves the endocrine gland changes in an intermediate position.

Hoping to gain some confirmation from a pathological viewpoint for this sequence, *viz.*, gastro-intestinal, endocrine, nervous changes, I sought Dr. Watson's opinion, which he gave as follows: " I cannot say definitely that the order you state is consistent with the pathological findings. This *may* be the order, but there is no pathological proof either in this case or in any other that I have met." On the other hand, as he pointed out, the changes found here may be explicable on the grounds of dementia præcox alone.

So many observations with reference to pellagra are now to hand that tentative efforts to classify and group them in some causal relationship are justified, even though such grouping fails to stand the test of time.

It must, I think, be admitted that in pellagra we are dealing, not with a disease entity, but with a syndrome, which may result from a number of different factors. The whole subject bristles with unsolved problems, and with one final question I must leave it. My question is this: Assuming that vitamin-B deficiency is a causative factor, then under what conditions does beri-beri occur, and what modifications of these conditions produce pellagra?

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Occasional Notes.

*Professor Eugen Bleuler.**

It is both an honour and a pleasure to write an appreciation of the work of Prof. Bleuler on the occasion of his seventieth birthday. The writer became much interested in the work of this eminent psychiatrist in the year 1910, being at that time engaged in the study of the negativistic reactions which many of his patients exhibited. It seemed unsatisfactory to regard negativism merely as a symptom carrying with it the suggestion of an unfavourable prognosis in those cases in which it was observed; it was a form of behaviour, and, as such, it was natural to wish to gain insight into the influences which impelled these patients to assume so curious and disconcerting an attitude towards the environment. Faced with this problem it can readily be understood how stimulating and helpful it was to meet with a series of articles in the *Psychiatrisch-Neurologische Wochenschrift* dealing with the psychological factors concerned in the production of schizophrenic negativism. This penetrating analysis—obviously the production of a great psychiatrist—not only illuminated the obscure problem with which it was immediately concerned, but provided weighty reasons for the investigation of the psychoses along psychological lines.

We associate the name of Prof. Bleuler in particular with the term "schizophrenia," which he suggested might be used to include the group of cases to which the term "dementia præcox" has hitherto been applied. This was much more than a mere change of name; it betokened a change of outlook, and opened up new avenues of approach to the problems of psychiatry. Though we in no sense wish to minimize the great significance of Kraepelin's clinical formulations, it appeared that the term "dementia præcox"

* *Psychiatrisch-Neurologische Wochenschrift*, May 30, 1927.

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