A CONTRIBUTION TO THE PATHOLOGY OF PELLAGRA.

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In August 1918 I was sent by the D.M.S., E.E.F., to No. 2 Prisoners of War Hospital, Abbassia, to investigate pellagra amongst the prisoners of war. In addition to other lines of work I collected the material on which I now wish to report.

With the collapse of the Turkish Army in Palestine the increase in the number of prisoners made the care of their health an important problem, therefore the D.M.S. appointed a committee to take over the work that I had commenced. Although I continued to collaborate with this committee I did not collect any further material as I was busy with other aspects of the same problem [5].

The symptoms of pellagra suggest that the common underlying defect is in the sympathetic nervous system. At the same time diet seems to be related to the onset of this disease.

The relation of these factors to the production of pellagra is given in the hypothesis that guided me in my work before the D.M.S. appointed his committee. The hypothesis was as follows: (1) Pellagra is associated with diets containing maize. (2) The experiments of Hopkins and Wilcock with rats fed on zein the chief protein of maize showed that the absence of tryptophane and lysin from the diet made it insufficient to maintain life [9]. That other proteins than those of maize may be inadequate to prevent the symptoms of pellagra is shown by the work of Wilson, who finds a relation between the "biological value" of the protein in the diet and the occurrence of pellagra [10]. (3) The symptoms of pellagra show a great similarity to those of Addison's disease and this similarity caused Sandwith to suggest in 1913 that pellagra may be due to an insufficient supply of adrenalin caused by a deficiency of aromatic amino-acids in the diet [6]. (4) The characteristic symptoms of pellagra are such as might be produced by abnormality in the activity of the sympathetic nervous system. Many quotations from Marie can be given in support of this statement but it is sufficient to point out (a) that all efferent fibres to the skin (vaso-motor, sudo-motor, etc.) are sympathetic in origin. Thus interference with the normal activity of the sympathetic system may lead to abnormal response to stimulation such as the skin symptoms produced by strong sunlight and pressure. (b) The sympathetic is inhibitor to the intestinal muscles but excitor to the intestinal sphincters, therefore deficient activity of the sympathetic will cause diarrhoea such as is found in pellagra.1

The early symptoms of pellagra are variable and evanescent, so much so that they suggest functional changes (showing over and under activity) and they might be ascribed to neurasthenia of the sympathetic nervous system. In advanced cases the symptoms suggest that the changes have become organic.

Adrenalin stimulates the activity of the sympathetic system by acting on the sympathetic nerve endings, but we do not know whether activity of the sympathetic

1 The above arguments are not conclusive because the diarrhoea may be caused by intestinal putrefaction which does occur in pellagra, and it is extremely difficult to disentangle cause and effect in such complicated conditions, but they were sufficient to form the basis for a working hypothesis.
requires a constant supply of adrenalin. Presuming such to be the case we see that excessive activity of the sympathetic system will require a larger supply of adrenalin and a deficient supply of adrenalin precursor will cause an earlier exhaustion of the adrenal medulla, therefore an earlier failure of the sympathetic system.

Thus we see that there may be two factors which may tend to cause pellagra:
(a) Deficient absorption of aromatic amino-acids.
(b) Excessive activity of the sympathetic nervous system, e.g., excessive sweating due to over-exertion in a hot climate.

THE MATERIALS.

In order to form a comparison I obtained adrenals and sympathetic nervous systems from cases some of which had been diagnosed pellagra and from others which apparently had not had pellagra.

In dealing with this material it must be remembered that an acute case of pellagra may not have lasted long enough to produce histological changes and that a case with some other diagnosis may have been a quiescent and unrecognized case of pellagra. The prisoners of war had all been subjected to the same conditions of diet and war-strain, thus the main difference was whether they showed symptoms of pellagra.

These complicating factors reduce the likelihood of finding marked differences and if the differences which I find in these few cases are genuine, much better results should be obtained with better-marked, long-continued cases such as I saw in Abbassia Asylum.

The adrenals were dissected out, cleaned from all visible connective tissue and weighed. Each adrenal was cut through its central portion from apex to hilum, so that a narrow strip was obtained from the most central portion. These two pieces (one right, one left) from each case were fixed in 3 per cent potassium bichromate containing 4 per cent formaldehyde, put through paraffin, embedded in the same block and cut.

The sympathetic chain of ganglia was dissected out, put through the same process as the adrenals and sections were made from various ganglia.

THE ADRENALS.

Earlier investigators have not found any distinctive histopathological changes in pellagra.

An assay of the amount of adrenalin was not attempted because it was thought that terminal infections would use up any adrenalin that might be present and thus mask any slight changes that might be due to the pellagrous condition.

Long continued insufficient supply of raw materials should lead to atrophy of the organ, hence the adrenals were weighed to see if their weights might give some evidence of atrophy.

Table I shows that on an average the adrenals from cases of pellagra are lighter than from cases who died from other causes. All cases of pellagra in which other diseases were proved to be present were excluded. Diarrhoea was considered to be a symptom of the disease unless true dysenteric conditions were present. Conjunctivitis was not considered to be a sufficiently severe complication to warrant a case to be excluded from the list of pellagrous cases.
Clinical and other Notes

The weights of the kidneys are given in order to show that the difference in weight is not due to the smaller size of the individual cases.

Sections stained with hematoxylin and eosin were examined, but no marked differences could be seen between the two sets of cases. In both sets the chromaffin tissue was small in amount; the cortical and medullary cells were shrunken. Such changes are explicable on the assumption that one is dealing with a population in which similar dietetic deficiencies are causing similar changes.

<table>
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<th>Case No.</th>
<th>Adrenals in grammes</th>
<th>Kidneys in ounces</th>
<th>Remarks</th>
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* Indicates those cases in which the sympathetic nervous systems were dissected out.

On the whole the group of specimens from the pellagra cases seemed to show greater shrinkage of cells and more marked hyperëmia. Hyperëmia of adrenals with increase in weight has been noted in other dietetic deficiencies [2], but the greater hyperëmia of the pellagra adrenals combined with their lesser weight will make the net weight of adrenal tissue even less in proportion to that of the non-pellagrous specimens.
Although these adrenal changes are not marked it would be interesting to obtain specimens from cases of longer duration, as one might find a definite fibrotic condition in such cases; that is, the functional condition of the adrenal in pellagra may become the definite organic condition of Addison's disease.

The Sympathetic Nervous System.

In contrast with the indefinite findings in the adrenals, the sympathetic nervous systems showed distinct differences. The most striking difference was that in the four pellagra cases the ganglion cells were plasmolysed, so that vacant spaces or large spaces with small shrunken cells were found, whilst in the other three cases the ganglion cells completely filled nearly all the spaces which they should occupy. Chromaffin granules were seen in the ganglion cells of both sets of specimens. If this condition of affairs were persistent, the non-medullated nerves belonging to the plasmolysed cells ought to atrophy and be replaced by connective tissue. Such changes may be shown in more chronic cases and in Addison's disease. The sections of the sympathetic nervous system were stained with van Gieson's stain in the hopes of showing some connective tissue, but no definite connective tissue fibres could be recognized.

The results obtained are so interesting in relation to the hypothesis that prompted the investigation that the matter is well worth pursuing further. As I shall not be in a position to obtain more material, I sincerely hope that someone more fortunate may be able to investigate the following problems.

1) Is the wasting of the adrenals in pellagra more marked than the wasting of the other organs?

2) Are the pellagra adrenals more wasted than the adrenals from cases of other wasting diseases and does fibrosis occur in the later stages?

3) Are changes in the sympathetic nervous system characteristic of pellagra or do similar changes occur in other diseases in which the sympathetic nervous system might be expected to be implicated (e.g., Addison's disease, shock, heat exhaustion, etc.)? In this connexion it is to be noted that W. Hale White found similar changes in the sympathetic ganglia [8]. Some of the results of derangements of the sympathetic nervous system are described by Langdon Brown [1].

Morse has found changes like those described here in two cases of pellagra [3], but the changes found in the central nervous system are like those produced by chronic toxæmia [4] or malnutrition [7].

Summary.

The results obtained suggest that (1) the adrenals are lighter in pellagra than in other wasting diseases; (2) most of the adrenals seem to be abnormal; (3) in pellagra the sympathetic nervous system shows definite histological changes.

It seems as if the Turkish prisoners of war had suffered from such nutritional changes that their adrenals were defective in activity, and that in those who had additional strain thrown upon them the sympathetic nervous system became exhausted with the production of the symptoms of pellagra.

During the course of these investigations I had the advantage of advice from many who know much more about pellagra than I do. Amongst these I wish especially to thank Lieutenant-Colonel P. S. Vickerman, R.A.M.C., Officer
Commanding No. 2 Prisoners of War Hospital, Captain J. Enright, R.A.M.C.,
Dr. J. Warnock, Dr. R. G. White, and Professor W. H. Wilson.
I also wish to mention the invaluable help that I received from my laboratory
attendant, Pte. H. Hulson.

REFERENCES.
[5] Report of a Committee of Inquiry regarding the Prevalence of Pellagra among Turkish
Prisoners of War. *Journal of the Royal Army Medical Corps*, 1919, xxxiii, p. 426,
508.

Lecture.

DEFENSIVE SCIENCE IN GAS-WARFARE.

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INTRODUCTION.

When I received from the Governors of this historic Institute their flattering
invitation to deliver an address to-night, the gloomy prospect of my shortcomings
was brightened by an occasional—a very occasional—cheering ray. Foremost
among such was pleasure that this distinction had been conferred upon an officer
of the corps to which I have the honour to belong, and whose Director-General
marks his appreciation of the compliment by his presence to-night—as I vainly essay
to follow the long train of distinguished predecessors to whom this opportunity
has been accorded.

The last occasion on which I spoke on this subject was on the voyage to Egypt,
when the adjutant posted a notice in these terms:

"Lectures.

Poisonous gas, by Major Lelean!"

To-night, by contrast, I am embarrassed by being allotted a title for my address
which is so attractive to a lecturer, and so dangerous to an audience, that an
all-night sitting would be required to deal faithfully with it. With your consent,