6. In monkeys the decrease of lymphocytes as indicated in differential blood-counts would appear to be more reliable in indicating tubercle infection than the tuberculin tests.

7. Less than ten virulent human tubercle bacilli can infect a child.

ABSTRACT OF DISCUSSION

DR. WILLIAM OPHÜLS, San Francisco: What were the anatomic findings in the monkeys that were so infected? Using these very small doses of tubercle bacilli for the infection, one approximates, I presume, the natural infection more closely.

DR. G. B. WEBB, Colorado Springs, Colo.: No observations were made on the tuberculous monkeys except as stated in my paper. We usually killed the monkeys immediately infection was recognized, as indicated either by a local lesion or glandular swelling.

LYMPHOCYTOSIS AS A SIGN OF CONSTITUTIONAL DERANGEMENT IN CHRONIC DISEASES OF THE DIGESTIVE TRACT*

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Of an extensive literature devoted to the rôle which constitutional factors play in the development of disease, only a small part deals with the digestive tract. In the discussion of gastro-intestinal diseases the local anatomic aspect dominates the conception of the morbid state. This conception is principally based on the demonstration of anatomic lesions at abdominal operations, which undoubtedly in many instances cleared up the true nature of a formerly obscure process. This applies, however, in particular to acute diseases; we cannot say as unreservedly that the demonstration of anatomic lesions has satisfactorily cleared up the pathogenesis of chronic diseases of the alimentary tract. In most of these chronic diseases anatomic lesions usually are the end-results of a pathologic process, but they do not necessarily indicate its working. For the understanding of its development, pathologic physiology promises better information than anatomic facts. It becomes more and more clear that disturbances of function are the causative factors of pathologic conditions in the alimentary tract: the irritative and the depressive disorders of motility and of secretion, spasm and atony, and increased and diminished secretion of the various digestive glands. When I discussed this topic last year,¹ I pointed out the necessity for studying the conditions which provoke the disorders of function. In this paper I intend to show that a general constitutional derangement very often forms the basis for the development of functional disturbances.

It has been demonstrated that the vagus and the splanchnic influence the activity of the digestive organs, although we know comparatively little of the way in which the functioning of these opposing nervous apparatus is physiologically regulated. On the

other hand, we have learned to recognize pathologic states or irritation of both nervous systems, the "vagotonia" and "sympathicotonia" of Eppinger and Hess.² Since these authors first differentiated the two conditions, other investigators have pointed out³ that often there are in a given case as many vagotonic as sympathicotonic symptoms, so that the sharp lines between the two states as originally drawn by Eppinger and Hess should be modified. Aside from this the inauguration of visceral neurology marks a decided progress. The knowledge of chronic vagus irritation has thrown considerable light on the pathogenesis of gastric ulcer, and one may expect that further investigation of the vegetative nervous system will clear up many unexplained points in the diseases of the digestive tract.

For the present discussion I wish to call attention to the fact that patients with vagotonic or sympathicotonic symptoms at the same time very often present signs of disordered internal secretions. The relation between disturbances of the ductless glands and those of the vegetative nervous system has not been safely established. Two years ago Dr. Cannon⁴ pointed out the possibility that the glands of internal secretion play a rôle in causing disturbances in the nervous system of the alimentary canal. Dr. Cannon's work deals especially with the effect of excessive secretion of the adrenals, which affects the alimentary canal precisely as splanchnic impulses affect it, by producing a total abolition of tone and a consequent inhibition of all activity.

There is much in the clinical picture of patients with chronic gastro-intestinal diseases which strongly suggests that the influence of disordered internal secretions, in particular of the thyroid gland, is frequently the primary factor which causes the derangement of the visceral nerves. Knowing the importance placed on lymphocytosis in disordered thyroid, I have tried to find out whether blood examinations would offer a firmer basis for such a conception. I have examined 140 patients who presented the different types of chronic functional and organic gastro-intestinal diseases, from plain constipation to gastric ulcer, combined with more or less numerous signs of vagus—or sympathetic irritation. I have purposely abstained from any attempt at classification. The point which I want to emphasize is the remarkable frequency of lymphocytosis which I have encountered in this series of cases.

In my classification of lymphocytosis I considered:

1. As normal a total of 10,000 white cells or less with a differential lymphocyte count up to 35 per cent.
2. As relative lymphocytosis a total white-cell count below 10,000 with a differential lymphocyte count above 35 per cent.
3. As absolute lymphocytosis a total white-cell count above 10,000 with a differential lymphocyte count above 35 per cent.

In the differential classification of lymphocytosis mononuclears and all transitional forms were excluded, while the small and the large lymphocytes counted together were given as lymphocyte percentage.

2. Eppinger and Hess: Die Vagotonie, Von Noorden's Samml. klin. Abhandl., 9 and 10.

3. For fuller information regarding these questions see: Hemmeter: New York Med. Jour., 1914, p. 101. Wolfsohn, J. M.: The Normal and Pathologic Physiology of the Visceral Nervous System, THE JOURNAL A. M. A., May 16, 1914, p. 1535.

4. Cannon: President's Address. Tr. Am. Gastro-Enterol. Assn., 1912, p. 10.

* President's address, read at the Seventeenth Annual Meeting of the American Gastro-Enterological Association at Atlantic City, N. J., June 22, 1914.

1. Kaufmann, Jacob: The Part Played by Functional Disorders in the Pathology of the Stomach, THE JOURNAL A. M. A., July 26, 1913, p. 251.

Of the 140 cases examined, 43 showed a normal lymphocyte count; 7 were on the border line; 16 showed absolute lymphocytosis, and 74 showed relative lymphocytosis. Of the latter 11 showed leukopenia, that is, a total white-cell count below 6,000, downward to 3,200.

Of the total number of 90 cases of lymphocytosis (16 absolute and 74 relative):

From 35 to 40 per cent. of lymphocytes were shown by 27.
From 41 to 45 per cent. of lymphocytes were shown by 18.
From 46 to 50 per cent. of lymphocytes were shown by 20.
From 51 to 55 per cent. of lymphocytes were shown by 20.
From 56 to 62 per cent. of lymphocytes were shown by 5.

The ninety cases of lymphocytosis represent 60 per cent. of all cases examined. Since a number of these patients reported only for mild temporary disorders and were examined as a routine, the 60 per cent of cases showing relative or absolute lymphocytosis must be considered very high.

The question is, What does lymphocytosis indicate? The examination of my patients soon made me realize that lymphocytosis is by no means as reliable a sign of exophthalmic goiter as it was formerly considered. Only a few of my patients presented symptoms which could be interpreted as caused by hyperthyroidism. I then found from the literature that during the last few years a different meaning had been given to lymphocytosis. Kocher's clinic, as Pettavel's⁵ recent publication shows, still adheres to the original conception of lymphocytosis as a direct result of hyperthyroidism. This view, however, has been challenged by a number of writers. Borchardt,⁶ Falta,⁷ and Maranon⁸ were among the first to point out that lymphocytosis is observed not only in hyperthyroidism but also in hypothyroidism, and, further, in disturbances of the other ductless glands such as the hypophysis, the adrenals, etc. These authors assert that the ductless-gland disorder is the primary disturbance, which in turn produces status lymphaticus, and they consider the lymphocytosis as a manifestation of status lymphaticus.

The linking of lymphocytosis and status lymphaticus has complicated matters so far as one forgets that we are dealing here with two distinctly different problems; first, with the relation of lymphocytosis and ductless-gland disorders, and second, with that of lymphocytosis and status lymphaticus. The definition of status lymphaticus is anything but clear. In literature we often find the diagnosis status lymphaticus merely based on the findings of blood-lymphocytosis, without any reference to the fact that these cases presented the hypertrophy of the lymphatic tissues or any of the other anatomic features, which Paltauf, and after him Kolisko, Bartel and Neusser have given as the main criterion of status lymphaticus.⁹ A good deal of confusion might be avoided if we followed Bartel,¹⁰ who proposed to confine the term "status lymphaticus" to the group of cases which are anatomically well defined by hypertrophy

of the lymphatic tissues, and differentiated this group from what he calls status hypoplasticus, which in a less restricted and broader conception denotes a general constitutional inferiority with more or less marked hypoplasia in various organs and with lymphatic systems which, although not hypertrophic, nevertheless show abnormalities. If we accept this differentiation it must be stated that according to Siess and Stoerck,¹¹ no lymphocytosis is found in true status lymphaticus, so that there is no justification for regarding lymphocytosis as an indication of status lymphaticus, as is done by most writers at present. If the findings of Siess and Stoerck are corroborated it must be declared an error to diagnose status lymphaticus merely because lymphocytosis is present. On the other hand, lymphocytosis is very frequently found in cases which answer Bartel's description of status hypoplasticus or whatever one may call this condition of general constitutional inferiority. Kahler¹² pointed out that lymphocytosis may be considered in a more general way as a manifestation of that constitutional derangement which in literature is differently described as lymphatism, lymphatic constitution, status hypoplasticus, general congenital asthenia, morbus asthenicus, infantilism, etc. This constitutional derangement is met very frequently. It may give rise to disturbances in various systems, a fact which accounts for the demonstration of lymphocytosis in so many different conditions. To quote only a few of a great number of publications: Von Hösslin¹³ and Sauer¹⁴ report the frequency of this blood-picture in all functional disorders of the nervous system which such patients are particularly prone to develop. Gudzent¹⁵ found lymphocytosis in chronic arthritis, so frequently associated with status hypoplasticus; Mohr¹⁶ in constitutional obesity, and Decastello¹⁷ in tuberculosis. The correlation of lymphocytosis and status asthenicus as developmental anomalies and predisposing factors for tuberculosis have often been discussed, lately by Bartel and Kraus.¹⁸

In the majority of my cases with lymphocytosis I noted a more or less pronounced tendency to asthenia or other manifestations of status hypoplasticus.

If it is permitted to conclude from all these findings that lymphocytosis may be taken as an indication of status hypoplasticus, the figures in my series certainly show that this constitutional derangement frequently forms a basis for the development of diseases in the digestive tract.

I have to come back once more to the question, What relation exists between lymphocytosis and disordered internal secretions? I quoted above the opinion of Kocher and others, who consider the blood-picture as secondary to the ductless-gland disorder. So far there is little proof for this contention and much may be said against it. In the first place it is difficult to understand how, as Borchardt and Falta assert, the same blood-picture should be produced by entirely different ductless-gland disorders—by decreased as well as increased thyroid secretion. I further call attention to Kocher's own reports which show that lymphocytosis remained unchanged in cer-

5. Pettavel: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1914, xxv, 748.

6. Borchardt, L.: Deutsch. Arch. f. klin. Med., 1912, cvi, 182.

7. Falta, W.: Deutsch. Arch. f. klin. Med., 1912, cvii, 103.

8. Maranon, G.: Boletín de la Sociedad Española de biología, 1911, v, 75, ref. Centralbl. d. exper. Med., 1912, ii, 158.

9. A very clear description of the physical characteristics of status lymphaticus is given by Haven Emerson in the Archives of Internal Medicine, January, 1914, p. 169.

10. Bartel: Status thymico-lymphaticus und Status hypoplasticus, Leipzig and Vienna, Franz. Deuticke, 1912.

11. Siess and Stoerck: Wien. med. Wchnschr., 1913, No. 8.

12. Kahler, H.: Ztschr. f. angew. Anat. u. Konstitutionslehre, 1913, 1, 139.

13. Von Hösslin: München. med. Wchnschr., 1913, Nos. 21 and 22.

14. Sauer, Hans: Deutsch. Ztschr. fr. Nervenhe., 1913, xlix, 447.

15. Gudzent: Deutsch. med. Wchnschr., 1913, p. 887.

16. Mohr: Verhandl. Cong. f. inn. Med., 1914.

17. Decastello: Wien. med. Wchnschr., 1914, p. 669.

18. Kraus, F.: Deutsch. med. Wchnschr., 1913, p. 194.

tain cases of exophthalmic goiter after the overactivity of the gland was successfully checked by operative treatment. This suggests that lymphocytosis is an indication of some factor other than hyperthyroidism.

In his monograph on status lymphaticus, Neusser¹⁹ suggests the possibility that the lymphatic tissues produce a secretion which acts as the antagonist of epinephrin, and that abnormal lymphatic tissues may cause a disturbance of this secretion, which in turn upsets the activity of the other ductless glands. More light will have to be thrown on this problem before we can speak of a causal relation. Until then it seems safer merely to record that lymphocytosis and ductless-gland disorders are frequently associated, or, to express it differently, that persons with status hypoplasticus are inclined to disorders of internal secretions. It seems that they are particularly predisposed to thyroid insufficiency, possibly on account of fatigue when more demands are made on them than their constitutional derangement permits them to bear.

In my series of cases, symptoms of thyroid insufficiency were decidedly predominant. I wish to mention here that in 1907 Dr. Sawyer²⁰ discussed the frequent relation of digestive disorders and thyroid disturbances and reported diagnostic blood-pictures. Dr. Sawyer designated his cases as incomplete forms of exophthalmic goiter. Most of my own cases presented symptoms which, according to the teaching of Hertoghe, Levi and Rothschild, Saenger and others, are the result of the thyroid insufficiency, so that instead of *formes frustes* of Graves, one should speak of *formes frustes* of myxedema, or as others have called it, of chronic benign hypothyroidism. The correct interpretation of the thyroid disorder is important for purposes of treatment. It is true that we should not differentiate too sharply, since it is known that overactivity as well as insufficiency of the thyroid may at different times occur in the same patient; and then, too, it is becoming more and more evident that thyroid disorders are rarely observed alone, but that as a rule they are combined with other ductless-gland disorders; yet there can be no doubt that in most cases one type of disorder is distinctly preponderant.

Of the signs attributed to hypothyroidism observed in my patients the most frequent symptoms pointing to retarded metabolism were: congestion of the liver associated with bilious attacks, headaches and migraine; tendency to fatigue, lack of ambition, mental depression, low blood-pressure, impaired circulation and cold extremities. In most of these cases a small thyroid gland was found which permitted palpation of the tracheal rings down to the sternum. Of the symptoms referable to the alimentary canal, I mention atony of the stomach and intestines with constipation and congestion of the mucous membranes causing a tendency to chronic inflammatory processes; when associated with symptoms of vagotonia, irritative disorders of the stomach, hyperacidity and hypersecretion, spastic conditions in various parts of the digestive tract from the esophagus down to the anus with all its sequelae, gastric ulcer, spastic constipation, mucous colitis, adhesions following inflammatory processes in the various organs and their mechanical results.

I wish to state that I observed some cases with symptoms of hypothyroidism in the digestive tract as

well as in other organs which showed no lymphocytosis, although their number was small as compared with the number which presented lymphocytoses.

In a number of cases presenting symptoms of hypothyroidism I had excellent results from the administration of thyroid. This was particularly instructive in cases of children suffering from malnutrition who were subject to gastric atony, constipation, congestion of the liver, headaches, etc., and who were freed of these disorders by thyroid medication. I observed cases of gastric hyperchlorhydria which had stubbornly resisted all other methods of treatment, and which then were relieved by taking thyroid. The same beneficial effect of thyroid therapy was experienced in other gastro-intestinal disorders when they were associated with chronic benign hypothyroidism.

I shall not discuss any further ductless-gland disorders and thyroid therapy, and I shall be very careful not to generalize. The report of successful thyroid treatment in my cases was merely meant to show that there are possibilities of causative treatment once we recognize the constitutional derangement and the disorders which it leads to. But valuable as such more specific forms of treatment are, there is a more important lesson to be learned from the present discussion; and this is, that the constitutional factor which I so often found at the bottom of chronic gastro-intestinal disorders should be given full consideration in the general management of such patients.

The periodicity which characterizes most chronic digestive disorders indicates that general conditions, such as constitutional derangements, are the decisive factors in the development of the disorder and not the anatomic lesions which are end-results. This is particularly evident in gastric-ulcer cases; and whether when treating them we shall succeed in avoiding recurrences will not depend so much on the employment of any special form of ulcer treatment, and in operative cases not on improved technic or new methods of operation, but it will depend to a much greater extent on our ability to regulate the patient's mode of living and on the patient's ability to observe general hygienic and dietetic principles and rules, which consider not only his local disorder, but in the broadest possible way his constitutional make-up, his mental state, his work, his habits, etc.

We are fully familiar with such conceptions for other diseases. It is generally understood that epilepsy develops on the basis of a constitutional disposition, and that this disposition must constantly be the object of treatment no matter whether the individual attacks are provoked by constipation, by the irritation of scar tissue, or from any other cause. There is no difference of opinion regarding the necessity of persistent hygienic and dietetic treatment in tuberculosis, if we want to succeed in fighting the ravages of the tubercle bacilli; and this is precisely the same situation which confronts us in many chronic gastro-intestinal disorders. We must emancipate ourselves from the narrow view which considers only the local disorder, be it ever so pronounced, and take into account the fact that a constitutional derangement is often the basis for the development of most of these local disorders, and that this constitutional derangement necessitates as persistent general treatment as it does in epilepsy, tuberculosis and other diseases. I hope that I have made this clear.

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19. Neusser: Zur Diagnose des Status Thymico-Lymphaticus, Vienna and Leipsic, W. Braumüller, 1911.

20. Sawyer: New York Med. Jour., July 15, 1907.