THE CLINICAL AND PATHOLOGIC RELATIONSHIPS OF HYPERPLASTIC AND NON-HYPERPLASTIC GOITER *

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The study of the clinical and pathologic relationships of the various types of goiter has of necessity been followed with the greatest interest in the surgical clinics. In a short paper it is impossible to review the various contributions to the subject. The following points, however, may be selected from the work done in these clinics: the clinical classification of the cases of goiter into simple or exophthalmic or equivalent terms, and the pathologic classification of the thyroids removed at operation into those with and those without sufficient hyperplastic or hypertrophic changes to characterize the gland; the recognition of toxic-goiter heart in a certain percentage of cases that are not diagnosed exophthalmic goiter and a less generally well-defined idea that the cardiac damage is only one of the manifestations of a general toxicosis; the finding of hyperplastic changes in from 70 to 90 per cent. of the thyroids removed for exophthalmic goiter, and the occasional presence of hyperplasia in glands removed from patients not having a history of notable toxic symptoms. Wilson, in 1908, after reviewing the available pathologic material from the cases which had been diagnosed as exophthalmic goiter, and in which operation had been done at St. Mary's Hospital, pointed out that 80 per cent. of the glands showed hyperplastic changes, and that, in general, the length and severity of the case history could be determined from the pathologic findings.

The relative constancy of notable hyperplasia in the thyroids of fully developed exophthalmic goiter, contrasted with the occasional failure to find this pathologic condition in glands removed from patients having an apparently similar clinical picture of this disease, and the rare finding of diffuse hyperplasia without accompanying evidence of thyrotoxicosis has led to much discussion and conflicting opinion regarding the specificity of this change.

In the latter part of 1908 a review of the clinical histories and the pathologic reports of our entire series listed as simple and exophthalmic goiters led me to the following conclusions: 1. We have at least two distinct, but very similar, types of thyroid intoxication, one associated with non-hyperplastic goiter, the other associated with hyperplastic or hypertrophic thyroids. 2. All cases having thyrotoxic symptoms with notable hyperplastic thyroids should be diagnosed exophthalmic goiter and that cases having thyrotoxic symptoms without notable hyperplastic thyroids should be classified with the cases of toxic-goiter heart, at least until we have still further evidence on which to subdivide these groups.

The main objection to these conclusions was the inability to make the clinical and pathologic diagnoses agree in about 10 per cent. of the cases. The lack of constancy in the clinical and pathologic relationship in mild and atypical cases could be easily explained. Our series, however, included (and I think this was true in other clinics) a number of cases of apparently typical exophthalmic goiter with exophthalmos and a pathologic report of adenoma, colloid goiter, adenomatosis, etc., without hyperplasia. A careful study of these cases demonstrated errors either in noting the presence of

exophthalmos or from incomplete pathologic examination in the majority of instances and a probability of errors in the remaining portion.

This led to the use, in writing the histories of the 3,207 cases that have come to operation since Jan. 1, 1909, of forms covering in great detail the points which might later prove of use in studying the development and course of thyrotoxicosis and its relation to the pathologic changes in the thyroid. Figures and signs having, so far as possible, fixed values have been used in place of descriptive adjectives. Observations of fact and opinion have been carefully distinguished. The clinical and pathologic findings have been placed in parallel columns without any comparison of notes on the part of the clinicians and the pathologists. Clinical records for statistical purposes have not been changed after the patient came to operation. This has made possible the compilation of statistics by clerks who are not in any way warped by preconceived ideas or a knowledge of factors other than those under immediate consideration.

Correlating the statistical data, we may safely come to the conclusion that exophthalmic goiter is a definite clinical complex always associated with hyperplasia of the thyroid, and that it should be sharply distinguished from the constitutional state or states that may develop with non-hyperplastic goiter. As a complete review of this material is beyond the scope of a short paper and the patience of the average reader, I have attempted to answer the questions brought up with the least possible amount of statistical data, using only the following factors: the age at which the goiter is first noticed by the patient; the age at which thyrotoxic symptoms developed; the presence or absence of exophthalmos, and the presence or absence of notable hyperplasia in the thyroid. It is my purpose to take up these questions with a full report in a series of papers.

The term "thyrotoxicosis" is here applied to the constitutional state associated with goiter. As a matter of convenience for quickly presenting the association of the clinical and pathologic findings, the constitutional symptoms accompanying goiter have been attributed to a toxemia the result of a disturbed thyroid function. As a temporary expedient the cases have been classified pathologically as hyperplastic and non-hyperplastic, and clinically as hyperplastic-toxic, hyperplastic-atoxic, non-hyperplastic-toxic and non-hyperplastic-atoxic. The glands showing marked hypertrophy have been included with the hyperplastic goiters. Following this classification for the 2,917 new cases coming to operation between Jan. 1, 1909 and Jan. 1, 1913, 42.8 per cent. are hyperplastic and 57.2 per cent. are non-hyperplastic. Of the hyperplastics 99.2 per cent. are toxic and 0.8 per cent. are atoxic. Of the non-hyperplastics 23.3 per cent. are toxic and 76.7 per cent. are atoxic.

While the association of the constitutional symptoms with non-hyperplastic goiter involves to a certain extent a personal equation, this is to a very limited degree true for the cases having hyperplastic thyroids. The estimation that 23.3 per cent. of the non-hyperplastic goiters are toxic is made on a very conservative basis.

Patients coming under observation with non-hyperplastic-toxic goiter give a history of having first noted the goiter at the average age of 22 years, and the evidence of intoxication at the average age of 36.5 years. The corresponding ages for hyperplastic goiter are, respectively, 32 and 32.9 years.

That non-hyperplastic goiter is noted ten years earlier in life than hyperplastic goiter, that fourteen and one-half years elapse between the appearance of non-hyper-

* Read in the Section on Practice of Medicine of the American Medical Association, at the Sixty-Fourth Annual Session, held at Minneapolis, June, 1913.

plastic goiter and the development of notable toxic symptoms, and that the constitutional symptoms were noted but a few months (between ten and eleven) later than the goiter in the patients affected with hyperplastic thyroid is alone sufficient to show that we are dealing with at least two distinct pathologic and clinical groups. That one is not the sequence of the other is self-evident.

Are all hyperplastic goiters coming to operation toxic? Throughout our series the number of cases in which the clinician failed definitely to note and attribute constitutional symptoms to the thyroid and which were later diagnosed hyperplastic goiter by the pathologists vary from two cases in 1909 to four cases in 1912. Two of these latter four cases were in children under 4 years of age and can be excluded in considering the hyperplasia of adults. The third case was that of a girl 15 years of age who gave a history of having noticed the goiter, periods of tremor, tachycardia and palpitation for nine months. These symptoms, however, were not attributed to the thyroid previous to operation. The fourth case was that of a woman 47 years of age who gave a history of having noticed the goiter for twelve years, rapid growth during the few months previous to coming to operation and a long train of symptoms, part of which might be attributed to thyroid intoxication. I have excluded a few cases that had small areas of hyperplasia in the thyroid because they are still under discussion by the pathologists. The majority of them had moderate toxic symptoms indicating that the activity of the thyroid is proportionate to the degree of the hyperplasia.

Is hyperplasia of the thyroid more prevalent in the first two decades of life than we have definite knowledge of, perhaps indicating a thyroid activity in response to some demand that cannot be considered far from normal? If so, is this hyperplasia of the thyroid to be sharply distinguished from the hyperplasia associated with exophthalmic goiter which develops at the average age of 32? I do not think that we can definitely answer these questions at present, though there is much evidence suggesting an affirmative answer, at least to the clinical side of the question.

Is the exophthalmos of thyrotoxicosis always associated with hyperplastic goiter? The pathologic reports fail to show the presence of hyperplasia in the cases in which exophthalmos was noted by the clinician, six times in 1909, four times in 1910, twice in 1911, and not in a single instance in 1912. Nine hundred and eleven new cases of goiter came to operation in 1912. In most of the exceptions to the rule previous to 1912, we have been able definitely to prove that there was an error in noting the presence of exophthalmos.

Should all toxic-hyperplastic goiters be included under the term "exophthalmic goiter"? Possibly there is a small group of cases which should not. That there is very little chance for error, however, in answering this question in the affirmative if we include only those cases coming to operation is indicated by the following facts: (1) Of the cases having diffuse hyperplasia of the thyroid coming to observation from one to three, three to six, six to nine, nine to twelve, twelve to eighteen, eighteen to twenty-four months, and over two years from the onset of toxic symptoms 50, 59, 67, 75, 80, 80, and 87 per cent., respectively, had exophthalmos (questionable cases excluded); (2) if we select from any period in our series twenty-five consecutive patients having hyperplastic thyroids and very mild toxic symptoms, over 50 per cent. had exophthalmos and if we select from the total number of patients coming to operation during 1911 and 1912 the twenty-five patients with non-hyperplastic thy-

roids having the most intense intoxication, exophthalmos is not noted in a single instance. It is quite possible that exophthalmos may be associated with non-hyperplastic-toxic goiter, but, if so, it is so rare that it must be in a way considered accidental.

Is the symptom-complex accompanying hyperplastic goiter to be directly attributed to disturbed thyroid function? While I have so considered it in this paper only as a matter of convenience for pointing out the association of the clinical and pathologic findings, and do not wish to get into a discussion of this subject at present, I do wish to call attention to a point in support of this theory that, so far as I know, has not hitherto been made, namely, that a person 22 years of age with an adenoma of the thyroid has a definite chance of developing a train of symptoms during the thirty-sixth year so similar to the symptom-complex associated with hyperplastic thyroid that the best-trained diagnosticians are constantly confusing the two conditions.

Can we associate the symptom-complex of non-hyperplastic-toxic goiter with any definite pathologic change in the thyroid? For the present I shall have to answer this question in the negative.

Correlating the statistical data herein given, we may safely come to the conclusion that exophthalmic goiter is a definite clinical complex always associated with hyperplasia of the thyroid and that it should be sharply distinguished from the constitutional state or states that may develop with non-hyperplastic goiter.

RECIPROCAL RELATIONS OF THE CLINIC AND THE LABORATORY IN MEDICINE*

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The clinic has been under obligations to the laboratory since the time of the first post-mortem descriptions of normal organs, and of pathologic changes in organs and tissues. Yet to-day one would pass over the founding of modern medicine by Rokitsansky, Cohnheim and Virchow on pathologic and histologic anatomy, to the consideration of the more striking relations of the clinic to bacteriology, parasitology, physiology, physiologic chemistry, experimental therapy and laboratory diagnosis. It is not that pathologic changes in tissues are unimportant, but in the newer fields of research there has been so rapid a development of methods applicable clinically to the accurate diagnosis and to specific therapy and prophylaxis of infective and parasitic diseases, and the correction and regulation of toxic and antitoxic metabolic disorders of a non-invasive nature, that the earlier pathologic investigations must be considered of a former era.

The laboratory has forgotten that the original stimulus for its efforts came from careful observers of clinical conditions. Without this it is doubtful whether the laboratory worker would have shown the patience of his clinical contemporaries, and it is likely that he would have taken himself in despair to other fields.

As a matter of fact, within a few years the clinic has swung far afield from the onward course of scientific medicine in the attempt to avoid the overwhelming strides of experiment and of laboratory application and

* Read by title, before the American Climatologist Association, Washington, D. C., May 8, 1913