LATENT SYPHILIS

AND THE

AUTONOMIC NERVOUS SYSTEM

BY

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PREFACE TO THE SECOND EDITION

THE additional subject matter contained in this second edition has deepened the impression that chronic syphilis produces many of its symptoms indirectly through the autonomic nervous system. The reason for this is found in the fact that the main lymph chain (where the virus lies more or less dormant throughout the latent period) and the main sympathetic ganglia lie side by side along the vertebral column. A change is, therefore, made in the title in order to emphasize this relationship.

Of the seventeen reviews of the first edition which have reached me, the majority are more favourable than ever I ventured to hope, and only two are hostile. I take this opportunity to answer these two reviewers, for we join issue on major principles.

In the chapter on cancer and syphilis I mention a cancer family where both parents and five out of six adult children died of cancer of the stomach. My reviewer says a responsible member of a hospital staff would never accept this diagnosis without pathological confirmation. There are on the one hand states observable with eyes and hands at the bedside —in this case epigastric tumours, hard glands in the

left supraclavicular fossa, and cachexia ending in the death of the patient with a clinical course which we know by experience to be characteristic of cancer of the stomach. On the other hand are states visible through a microscope. Somehow or other my reviewer believes that these latter are of a higher scientific order, and he will not accept a clinical diagnosis as true unless it is confirmed by microscopical section. The Registrar-General, however, accepts scores of such diagnoses every day and few question their truth. The point at issue, therefore, is whether or not a fact seen at the bedside is as true as one seen in a test-tube or down a microscope. The reader must choose for himself.

Again, one of my cases of dysphagia and anæmia was the grand-daughter of a syphilitic, and this basis for diagnosis is described as speculative and improbable. The facts are, however, that this patient had many of the signs which enabled me to diagnose syphilis with confidence, and, as the event proved with accuracy, seven years earlier than was done elsewhere.

To the orthodox the only link with this disease was the grandfather, and the diagnosis was persistently rejected by the highest authorities until Argyll Robertson pupils and insanity arrived almost simultaneously to close the patient's social career.

One friendly critic says I mention no failures. As, say, in locomotor ataxia, so in visceral syphilis,

'cures' are only obtainable in the earlier stages—but if my general practitioner readers will accompany me to the nebulous confines of syphilis—that penumbra of doubt where disordered function is not yet set into a physical sign—many tragedies such as that just mentioned will be avoided.

Several reviewers do not believe in the granular virus stage of the life cycle of *Treponema pallidum*. I can only beg them to read again the leader from the *British Medical Journal* which I quote in full. The disease is only truly latent when the virus is confined to the lymph-glands without any inflammatory reaction. Between the true latent stage and the evident stage there is a period of years when no laboratory method can detect the disease, and we have here an illustration of the limitations of mechanical diagnosis. Those who depend on laboratory tests will have to wait until the majority of cases are incurable—but the family doctor alert from the first because of his knowledge of past and family history can check the disease by acting on the strength of the small and inconclusive signs which are described herein.

January, 1937.

PREFACE TO THE FIRST EDITION

IT now appears to be accepted that *Treponema pallidum* passes through a developmental cycle —an active spiral stage with dormant granular alternation. Clinical descriptions of syphilis have recently concerned themselves with the manifestations found with spirals and a positive Wassermann reaction. The constant association of other clinical states with a history of syphilis compelled the adoption of such terms as ' parasyphilis ' and ' metasyphilis '. Here spirals are not necessarily found, nor is the Wassermann reaction often positive. It is probable that these states result from the presence of the granular virus.

Another important landmark is Nabarro's insistence on the transmissibility of syphilis to the third generation. I have acted on this belief for several years, although intermarriage and the possibility of intercurrent infection make the case difficult to prove. A recently met sequence is typical—grandmother blind from specific iridocyclitis ; mother a chronic asthmatic and bronchitic, with unequal pupils relieved by mercury and iodides ; daughter, aged 10, had fits, and improved under Hutchinson's pills. The important thing for the family doctor is that the therapeutic test is satisfactory.

Now that the granular form of the virus is demonstrated, research must commence from another point. We must inquire what clinical states are attributable to this form as contrasted with the spiral. The length of time required for such a study, and the value of family history in this connection, make this research the peculiar province of the family doctor. The essays which follow are the first part of such a clinical research. Incomplete in many respects, and with much repetition of what the writer regards as fundamentals, they may excite some interest in the field where the therapeutic response is so gratifying to all concerned.

My thanks are due to the Editors of *The British Medical Journal*, *The Practitioner*, and *The Clinical Journal*, for permission to reprint articles from their pages ; and also to Dr. Erie Evans for reading the proofs.

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CHAPTER I

INTRODUCTION

BECAUSE syphilis is a protean disease its exact description is difficult. It can be understood only from a study of its history and pathology, which provide a formula applicable to the numerous cases which respond to treatment with mercury and iodides, but which do not show pathognomonic symptoms. History shows the remarkable evolution of the disease. Its virulence, revealed by the high primary mortality of the great European pandemic in the fifteenth century, gradually decreased. Within living memory gummata and bone necrosis have virtually disappeared from the out-patient departments of our hospitals. Indeed, the minor character of the disease to-day has led some to believe that it will soon be obsolete. L. W. Harrison[1] expresses the present position thus: "The tendency of syphilis is to become latent so far as outward manifestations are concerned. Animal experiments teach us that syphilitic infection is latent from the first in a definite proportion of cases, so that non-appearance of a chancre is poor evidence of non-infection." Gürich[2] also says, "It seems as if

the whole aspect of syphilis has changed," when he records a progressive rise in organic syphilis from 3 per cent of all autopsies in 1919 to 5·7 per cent in 1924. It follows that we should be watchful for these new forms.

Pathology gives the key to the change. It lies in the increasing power of the body to confine the virus to the lymphatic system, whence, however, it may emerge to attack the host, with the production of either temporary or permanent disability.

The secondary stage is brought to an end by a general lymphadenitis. In Martland's[3] description of the clearing of the spirochætes from the blood occurs the passage: " The lungs, on account of their great capillary area, have received a greater dosage (of spirochætes) than any other organ and must clear themselves in a different way . . . many organisms pass by lymphatics to the peribronchial and mediastinal glands. The latter become reservoirs for storage of spirochætes." Klotz[4] writes, " It is from two main lymphatic drainage beds, the thoracic and the abdominal, that the syphilitic virus comes to be distributed to particular segments of the aorta. It is not difficult to demonstrate chronic mediastinitis, which has a distinct course along lymph-channels to and from glands, but it is unusual to find glands enlarged to such a degree that they would attract attention clinically or pathologically. By thus localizing in the mediastinum, the syphilitic virus has an opportunity of attacking to a greater or less degree the important visceral contents of the thorax." Carey Coombs

summed up the lymphatic hypothesis in these words: "The peri-aortic origin of (syphilitic) aortitis is recognized. The cellular infiltration that is its distinctive mark wells out of the mediastinal lymphatics in the direction of the aorta, and is piled up on the outer surface of the adventitia."

This newer pathology of syphilis has been applied to internal medicine only in the fields of cardiology and neurology. It is difficult to understand why, because, admitting some degree of selectivity, the œsophagus, and vagus in the thorax, and the sympathetic ganglia in the abdomen can hardly escape so widespread and destructive a process as the perlymphatic infiltration described by the foregoing authors. Indeed, it is so reasonable on pathological evidence to attribute nervous dysphagia and dyspepsia, spastic colon, chronic abdominal pain, and the like, to syphilitic infiltration of the sympathetic system, that writers on these subjects should at least be at some pains to offer a better founded etiology.

From the field of animal experiment two discoveries are of outstanding importance to the clinician: (1) Superinfection has been proved possible; (2) Infection by a latent case may not, and probably will not, produce a chancre or exanthem, but only chronic proliferating lesions.

Having regard to its chronicity, and its transmissibility to offspring, syphilis is the commonest single disease which calls for treatment to-day. The slow development of aortitis, and the earliest onset of tabes, can be checked only if the family doctor is armed with

a knowledge of the pathology, and has the courage to make a diagnosis. But if a case is allowed to progress until it enters the circle of the heart or nerve specialist, the diagnosis becomes evident and the damage incurable, and, what is more important, the early signs are not put on record. It is necessary to insist that a diagnosis of latent syphilis can be made to-day, though this was not possible before the discovery of the spirochæte and the growth of exact pathology which followed. The present generation of teachers seems to have inherited a tendency to deplore a facile assumption of a diagnosis of syphilis in cases of obscure origin ; so much so that there is actually a prejudice against applying to clinical teaching recent discoveries in pathology and animal experiments. The fact remains that mercury and iodides are valuable in other conditions than classical syphilis, and the necessity remains to define this class so as to rationalize the treatment.

It is customary to demand that one of three standards be satisfied before diagnosing syphilis : (1) The Wassermann test ; (2) Demonstration of spirochætes ; (3) Gross pathognomonic lesion.

Trained to apply these standards rather than to reason from pathology and biology, the medical student is unwilling to make a diagnosis of syphilis in their absence. However, experience, and a slowly won knowledge of family and personal history, lead him in time to treat specifically a more numerous and less-defined class. The success of such treatment is the basis of the belief that there exists a large number

of syphilitics in whom the infection is low-grade, the Wassermann test negative, and spirochætes no longer demonstrable. This belief is strengthened by critical examination of the aforementioned orthodox standards. The Wassermann reaction is negative in 50 per cent to 60 per cent of latent cases. L. W. Harrison[5] collected a series of 6829 latent cases with + W.R. in 45·6 per cent. At the second laboratory conference in Copenhagen (1928) the Wassermann test was compared with other tests, and was found to be positive in 208 out of 496 cases of syphilis. The clinical diagnosis of syphilis must have been indisputable, because there was a parallel series of non-syphilitic cases, yet only two-fifths gave a + W.R.

Now it is easier to suspect latent syphilis than to prove its presence, but the pathology of the disease makes it certain that a large indefinite class exists. The infection does not end abruptly ; the spirochæte and host even appear to reach a stage of symbiosis, for many old syphilitics live to a great age and enjoy good health, as if they were protected from intercurrent infection. In others the issue is not so happy. The localized lymphocytic reaction becomes leucocytic and spreading, possibly producing symptoms. Only gross changes will produce recognizable clinical signs, and the sense of discomfort felt by such a patient may be dismissed as functional if family history, minor signs, and the pathology of latent syphilis are disregarded. Illustrating this is the case of a woman, aged 50, who complained of ' indigestion ' brought on by exertion and who

gave a history of mild muscular rheumatism. On examination were found blood-pressure 190/100, absent knee-jerks, W.R. negative. Her father died of locomotor ataxy and her mother of tumour of the brain. She was an only child. She was completely relieved by bismuth injections and mercury and iodide by the mouth, and can now walk seven or eight miles in a hilly country. A pathologist told the writer in 1931 that he would not accept a diagnosis of syphilis in the absence of a positive Wassermann reaction or gross lesions. His view is probably not shared by the majority of pathologists, but it closely reflects the attitude of many teaching physicians. What is a general practitioner to diagnose in the case of the child of a tabetic whose cardiac symptoms are relieved by mercury and iodides? His function is to relieve symptoms, and he claims to do so in this class of patient, neither empirically nor apologetically, but on a foundation of reasonable diagnosis. So much for the first of the diagnostic standards. It is clearly improper to withhold specific treatment merely because a Wassermann test is negative.

The second standard—demonstration of spirochætes—also has grave limitations. The organism is easily shown in primary and secondary lesions, but with difficulty in the tertiary stage. In a personal communication a pathologist says: "The demonstration of spirochætes in tertiary syphilitic lesions is said to be difficult and uncertain even in gummata." The process of staining is so tedious that it seems doubtful whether the enthusiasm in this branch of pathology

shown by the late A. S. Warthin will be equalled. Critics of his work have shown the perivascular infiltration to be due to a lymph-borne rather than blood-borne virus. This is a minor point for the practising physician. In a series of sections from latent cases stained for spirochætes for the writer, the control used was liver of a congenital syphilitic known to contain large numbers of spirochætes. It would clearly be fairer to use as control the corresponding tissue from a known tertiary syphilitic. When we remember that the *Treponema pallidum* has been demonstrated only once in locomotor ataxia (Noguchi, 1913), the almost unattainable height of this second standard is seen; Saleeby[6] (1926), in the testes from 40 syphilitic cadavera, found the *Treponema pallidum* in only one case—a stillborn; Pearce and Brown[7] (1922) found the *Treponema pallidum* microscopically in only 3 of 29 virulent glands of syphilitic rabbits.

But there is a more important consideration. To-day it is taught that the spiral is the only form assumed by the virus, and all the pathological findings are attributed to this. Evidence is accumulating to support McDonagh's hypothesis of a spore stage in the life-cycle.* Involution forms were seen by O'Farrell and Balfour[8] (1911) after injection of '606'. They thought they were resistant spores. Levaditi and his colleagues[9] (1922) made similar observations, and at the same time pointed out the very high infectivity of glands of rabbits suffering from experimental

* See note on p. 15.

syphilis, and the rarity with which the spirochæte is seen in the glands. The practitioner looks to all this research for help to relieve his patients, and for practical purposes it is clear to him that he must be prepared to diagnose syphilis, not only in the absence of a positive Wassermann reaction, but also in the absence of demonstrable spirochætosis.

The third diagnostic standard—namely, gross pathognomonic lesions—is open to similar criticism. All pathologists agree that scattered areas of chronic inflammation are found in old syphilitics, and all agree that the gummatous process may be diffuse and microscopic, as well as localized and visible to the naked eye. But if they are confronted with such a specimen, few will commit themselves to a diagnosis of syphilis because of the difficulty or impossibility of showing up the spirochæte. Their attitude is correct, for they truthfully say that identical appearances may be produced by other organisms—notably tuberculosis, and even by the toxins of chronic intestinal stasis. Indeed, they argue that the body can only react in one way to any chronic infection, and that therefore the perivascular lymphocytic infiltrations which Warthin[10] (1918) describes cannot be pathognomonic of syphilis. Nevertheless, L. W. Harrison[11] says, " A more careful search such as Warthin conducted might show diffuse infiltration to be the predominant lesion of syphilis."

This difference of opinion throws into relief the importance of observed familial traits and the value of the therapeutic test. Of the latter, Allan Todd[12]

(1926) says: "Fundamentally this 'syphilitic arthritis' is cured by specific treatment. This last is a very important criterion in diagnosis, and is a much more important piece of evidence than any Wassermann test."

In clinical research either of two methods may be adopted: A group of signs may be noted and the cause sought, or the victims of a known pathogenic agent may be observed and their symptoms enumerated. It seems to me that the time has arrived to apply the second method afresh in the case of syphilis, especially as the lymphophilic character of the virus is becoming more securely established.

That our methods of diagnosing chronic syphilis call for revision is proved by a recent article by Moore.[13] Of 105 cases of luetic aortitis found post mortem at the Johns Hopkins Hospital, only 4, or 3·8 per cent, had been diagnosed during life, yet 52 had lesions which should have been found by physical examination. This in one of the foremost teaching hospitals of the world!

The approach to the clinical aspect of latent syphilis should be along the trail blazed by Kiss. He has shown that the paravertebral sympathetic nerves actually traverse lymphatic glands in addition to being in wide and close topographical relationship. We have already seen that the secondary stage of syphilis is brought to an end by a general lymphadenitis and that latent syphilis is essentially a chronic lifelong lymphadenitis. The destructive effects of this lymphadenitis on the aorta and central nervous system are

well known and defined, but none are recognized in immediate anatomical relations—most important of which are the autonomic nerves. Resection of these nerves is being increasingly used for pylorospasm, megacolon, retention of urine, and arterial occlusion, and evidence of disease in the removed chains and ganglia is well established. Lawrence says that the cellular infiltrations are consequent on emotional hyperæmia—but it is not unreasonable to ask surgeons to exclude a common chronic disease centred in the immediate neighbourhood of the nerves, before attributing scars to emotion. Inadequacy of the sole diagnostic standard in common use—the Wassermann reaction—is the real cause of this peculiar mentality.

Latent syphilis demands direct exclusion in chronic dysfunction of the autonomic system whatever the clinical manifestation may be. The same anatomical facts apply particularly to the œsophagus, the roots of the lungs, the roots of the mesentery, the pancreas, and the suprarenal bodies.

Some of Kiss and Botar's plates showing these anatomical relationships are reproduced here (*Figs.* 1–3). The authors sum up their paper in the following conclusions :—

1. Many lymphatic glands are in close topographical relationship with ganglia, trunks, and branches of the sympathetic nerves.

2. Pathological changes in the glands (chronic hypertrophy, acute inflammation, etc.) can certainly exercise a pathological influence on the ganglion cells and fibres of the sympathetic nerves.

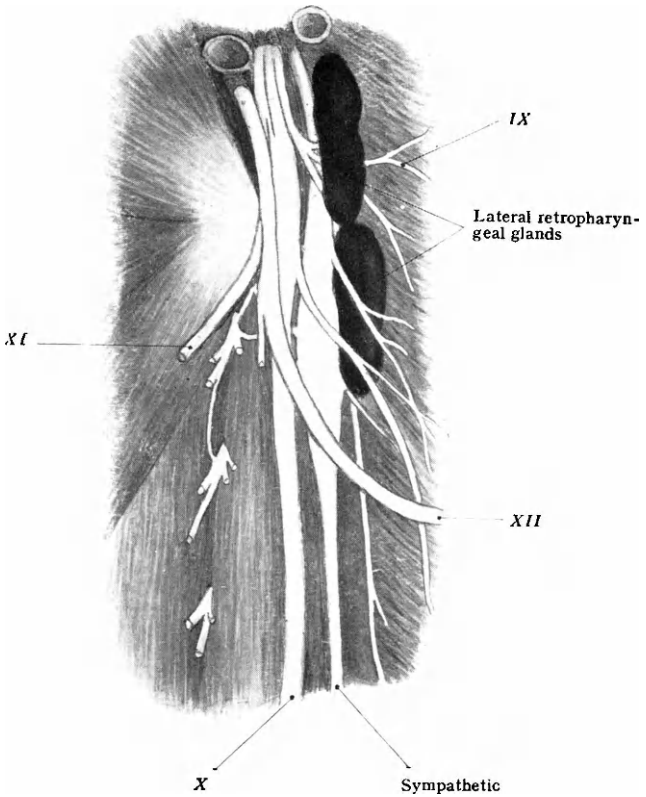

FIG. 1.—Relationship of the lateral retropharyngeal glands with the superior cervical ganglion of the sympathetic and the vagus.
(*After Kiss.*)

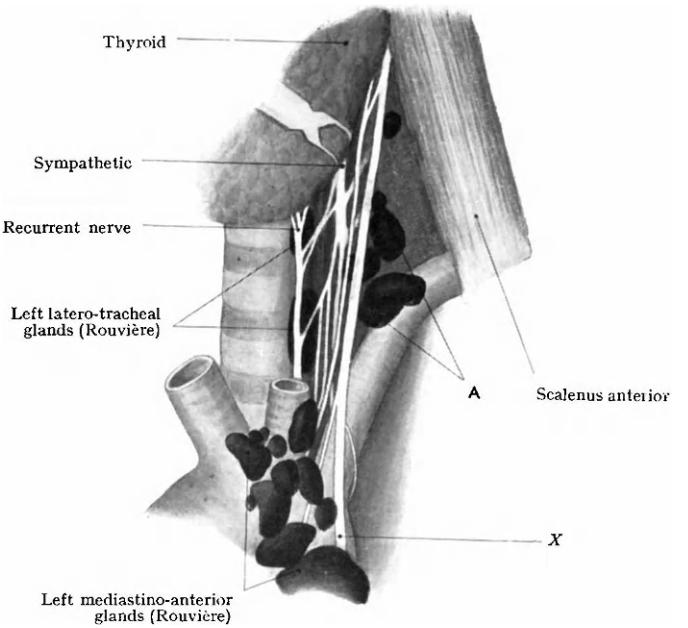

FIG. 2.—Relationship of the left anterior and recurrent mediastinal glands with the left vagus, recurrent, and sympathetic nerves.

The most external glands of the left latero-tracheal chain (A) have been diverted laterally. (*After Kiss.*)

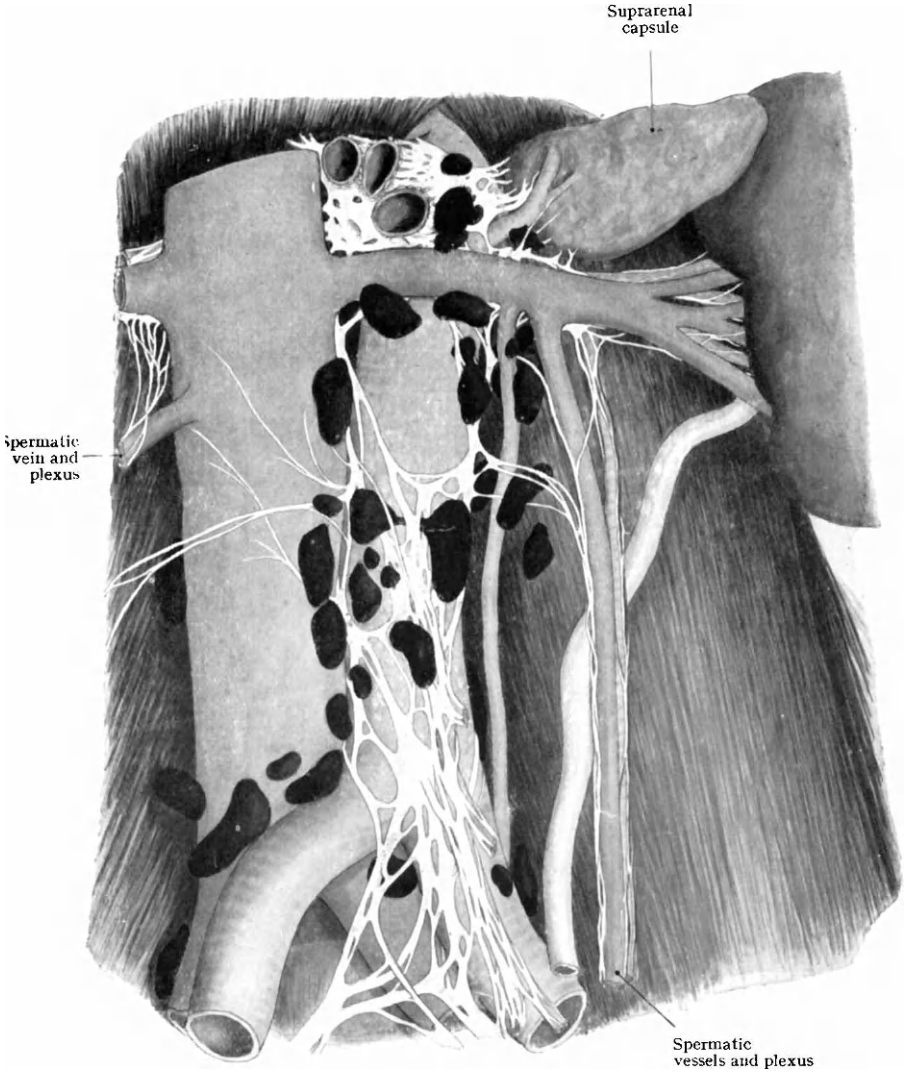

FIG. 3.—Mesenteric lymph-glands and the sympathetic. Showing the relationship between the lymph-glands in the region of the abdominal aorta and the lumbo-aortic plexus of the sympathetic. (*After Kiss.*)

3. In operations involving the glands (tumours, adenectomies, etc.) the surgeon should be careful to respect the plexuses and branches of the neighbouring sympathetic nerves. Many post-operative complications are due to injuries of these nerves.

Regarding conclusions (1) and (2), we may pause to ask what are the common causes of chronic lymphadenitis. These will be the indirect causes of sympathetic irritation and dysfunction, and their removal will render unnecessary many surgical sympathectomies. First, there is an ill-defined mass of clinical material where palpable glands are found in axillæ and groins without focal lesions. If outlying glands are thus palpable we may assume for purposes of treatment that the more important central paravertebral glands share in the enlargement and that the whole body is the victim of a chronic infection. The causative organism may be impossible to find. This condition is illustrated by the large rheumatic class where palpable epitrochlear, etc., glands are often found.

In the second class, less numerous but by no means negligible, are the two major lymphophilic diseases, tubercle and syphilis. Although the microscopical unit (giant cell, surrounded by inner zone of endothelial cells and outer zone of lymphocytes) may be indistinguishable in the two diseases (it has been said that a more typical tubercle is produced by syphilis than by tubercle) there are certain broad distinguishing principles. For the purposes of this paper only

one will be mentioned. In syphilis the adenitis is plastic—an ebb and flow of lymphocytic infiltrations, always mobile, but extremely slow. New vessels replace those obliterated by endarteritis. Organization ends in fibrosis, until at last, as in the case of aortitis, the blood-supply of neighbouring structures is so diminished that both structure and function are altered. Tuberculous lymphadenitis has never been accused of being the cause of aortitis, and for the same reasons it need not be seriously considered as a cause of the chronic dysfunctions of the sympathetic system. It does not possess the strangling power of the syphilitic variety. Furthermore, while tuberculous neuritis is a curiosity not to be thought of in routine practice, in every case of chronic neuritis it is an essential step to exclude syphilis. If the *Treponema pallidum* can so affect the somatic nerves, can we be sure that it has not a similar affinity for the sympathetic system ?

We must reflect that this is not a problem soluble by so-called scientific methods : it is one in which logic and critical philosophy are necessary to preserve us from error. It is amazing that a perusal of the writings on diseases of the vegetative system during recent years fails to discover any reference to syphilitic adenitis as a common remediable cause. Surgery can only suggest neurectomies ; medicine is content to advise antispasmodics and diathermy.

Possibly long familiarity with individual patients and with their relations, such as is only obtained in general practice, is necessary to recognize the slight

but persistent and slowly changing signs of chronic Wassermann-negative syphilis.

If this slow chronic inflammation does but disturb the normal physiology of the parts affected, we have the following clinical states :—

In the thorax : (1) Asthma ; (2) Spasms of the œsophagus (the dysphagia and anæmia syndrome) ; (3) Vasomotor changes in the upper limbs and head ; (4) Deep-seated, indefinite localized pain.

In the abdomen : (1) Spastic states of the bowel, such as spastic colon ; (2) Abdominal pain, variable and indefinite in type—the sympathetic being the sensory nerve to the bowel, localization is not exact ; (3) Vasomotor changes in the lower limbs ; (4) Affections of the endocrine glands, of which I propose to mention only the adrenal body ; (5) Plastic peritonitis and adhesions ; (6) Tender aorta.

It is not suggested that chronic syphilis is the sole cause of all these clinical states, but it must be evident as a logical sequence of the foregoing pathology and anatomy that the differential diagnosis of syphilis is essential in all those disturbances of the sympathetic which occupy so much space in medical literature to-day, and which, so far as can be seen, have never been connected with chronic syphilis. Diseased chains are treated by the crude but effective method of excision.

Expressed in another way the problem is this : Syphilitic lymphadenitis is established as the cause of aortitis and therefore of aneurysm. Does every other immediate anatomical relation escape this destructive

process, or can we find parallel lesions in the œsophagus, the roots of the lung and mesentery, the adrenal body and pancreas, and, most important of all, the autonomic system? If so, what are their clinical signs? It is the writer's opinion that such lesions exist, and that they are remediable causes of nervous dysphagia, of asthma, of chronic abdominal pain and digestive disturbances, of endocrine dysfunction, and of all the clinical states attributable to autonomic imbalance.

Chapters II to VI are concerned with diseases of the thyroid, asthma, and vasomotor disturbances, and the place of syphilis in the etiology is indicated in the table below.

Disease	Total Cases	Syphilitics	Doubtful Syphilitics	Percentage
Diseases of thyroid ..	196	18	48	33·7
Asthma	44	7	9	36·3
Angioneurotic œdema ..	13	6	—	46
Purpura	6	4	2	100
Blanching of extremities	11	2	1	27·2
Congestion of extremities	11	3	4	63·6
Claudication	4	2	—	50

These proportions are high, but they reflect the experience of the writer during fourteen years.

Probably the percentages in the last column are indeed higher than would be found in other parts of the country, but a small and ancient seaport, once a military headquarters and a naval station, with a strong seafaring section in its population, is a favourable site for the study of the remote effects of lues. Moreover the writer submits that these clinical

findings correspond to what would be expected as a logical result of anatomy and of the pathology of syphilis.

If Osler's estimate that 1 in 10 of the population of Britain is syphilitic is correct, the findings will not be without general applicability. The argument in general refers to all conditions for which sympathectomy is practised or recommended.

Developmental Cycle of *Treponema pallidum*

(*Brit. Med. Jour.*, 1933, Sept. 9)

The view that spirochætes pass through a developmental cycle is not new. Leishman, in a series of papers from 1909 onwards, produced evidence that in the tick the spirochæte of African tick fever broke up into a number of granules from which the spirochæte could again develop. Balfour described granule formation in the case of *Treponema pallidum*: some workers have gone further and elaborated quite complicated life-cycles for the virus of syphilis. The work of Levaditi and his colleagues[14] on this question began in 1927. It had as its starting-point the well-established observation that the peripheral lymph-glands of rabbits with scrotal syphilomata, although almost invariably virulent, contain no demonstrable spirochætes. As a result of their investigations, which approached the subject from both the biological and the histological point of view, they concluded that the spirochæte did not represent the whole story of the virus of syphilis. Continuing their studies Levaditi and his collaborators[15, 16] have shown that the changes in and around portions of virulent lymph-gland, implanted under the scrotal skin of rabbits, occur in two distinct and definite phases. During the first of these, lasting some thirty to forty days, the grafted tissue becomes necrotic, is invaded by polymorphonuclear leucocytes, and is surrounded by a banal inflammatory reaction; the most minute search reveals no spirochætes. The second phase has quite a brusque onset. Spirochætes appear in the inflammatory tissue surrounding the implanted lymph-gland, multiply rapidly, and invade the necrotic graft. The histological aspect of the lesion also undergoes a dramatic change, and now takes on the specific appearance of

a syphiloma, the granular polymorphs and large mononuclear phagocytes being replaced by lymphocytes and plasma cells arranged in dense formation around the newly formed vessels.

Levaditi considers two hypothetical explanations of these facts. Either the spirochæte is present in very small numbers in the virulent lymph-gland—the numbers being so small as to render its demonstration difficult or impossible, and a long latent period being required to allow it to multiply sufficiently to be demonstrable microscopically—or it exists in an invisible form which is capable, in a suitable environment, of developing into the visible spirochæte. He favours the latter hypothesis. Profiting by an observation of Schlossberger[17] that in mice inoculated under the skin of the back with syphilitic material the central nervous system becomes virulent but contains no demonstrable spirochætes, Levaditi and his colleagues[18] have reinvestigated the question. The findings of their latest investigation entirely support their earlier experiences. The most minute search failed to reveal spirochætes in the brains of mice previously inoculated subcutaneously with syphilitic material, yet an emulsion of such a brain introduced under the scrotal skin of rabbits produced typical chancres. Here again a histological study of the lesions revealed the same two phases, the first a banal inflammatory one and the second that of a specific syphiloma. Again the spirochætes appeared first in the surrounding inflammatory zone, in close relation to the newly formed vessels, and invaded the necrotic brain tissue; the change in the histological structure of the lesion was subsequent to the appearance of spirochætes. The evidence which these workers have obtained lends strong support to the conception that the virus of syphilis passes through a developmental cycle of which the spirochæte is but one phase.

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CHAPTER II

SYPHILIS AND DISEASES OF THE THYROID

IT is not at first apparent why the thyroid should be spoken of in this connection. It is, however, affected in three definite ways: (*a*) It is part of the mechanism of defence to infection; (*b*) It is so intimately affected by sympathetic irritation that authors have been doubtful as to whether the primary disease in hyperthyroidism is in the gland or in the sympathetic chain; (*c*) The thyroid compensates for chronic adrenal exhaustion.

MacDonagh pointed out, and Warthin stressed the fact, that the adrenal body is commonly affected in chronic syphilis, and furthermore that affection of the adrenal body is characteristic of the disease in the female. In his *Sex Differences In Syphilis* Warthin states that to find evidence of syphilis in the male one examines the aorta and testis, whereas in the female one examines the adrenal body. The bearing of this fact on the prevalence of thyroid disease in the female deserves closer study.

Before dealing further with the relationship of chronic syphilis and disease of the thyroid it is necessary to pass in review some of the main facts of thyroid pathology. This forms one of the most difficult chapters of medicine because our knowledge

is incomplete and many of the experimental findings are apparently conflicting. There are, however, three large classes of thyroid disease: (1) Epidemic; (2) Endemic; (3) Sporadic. Consideration of the first two groups helps us to understand the third.

1. Epidemic Goitre.—Many epidemics of acute goitre have been recorded but in no case has a satisfactory cause been demonstrated. For instance, in 1923 there occurred an epidemic of acute goitre in one only of nine houses which constituted a children's home. The fullest investigation failed to reach a more satisfactory conclusion than that the epidemic was the result of some unknown infection. McCarrison reports an epidemic among Europeans temporarily resident in an endemic district. Several epidemics have been described in continental military stations. These epidemics disappear spontaneously when the cause removes itself.

2. Endemic Goitre.—Endemic goitre differs from epidemic in that its cause is not transient but a feature of a district. Its distribution is geographical, its chronicity produces secondary changes — fibroses, nodules, degenerations.

Many elements have been shown to play a large part in the production of endemic goitre. It was traditionally ascribed to bad water, both in early European and Chinese medicine. Dramatic cures followed treatment on these lines. Birscher (quoted by Breitner) cured a whole Swiss village by bringing in a new water-supply. But it was elsewhere shown that water was not the sole vehicle of infection.

Breitner mentions dogs taken from Berlin to a goitrous village, which became goitrous although kept on pure water. Similarly, rats kept in a cellar became goitrous, while control rats kept in sunlight remained healthy. Calcium and food vitamins have similarly been demonstrated as contributory causes of goitre.

The role of iodine is well illustrated in Napoleon's classical map of the goitrous districts of Switzerland. In Waadt there was no goitre ; in Friebourg, separated by a river, goitre was endemic. In a village on the Waadt side of the river, which belonged politically to Friebourg, there was goitre. Each town derived revenue from the taxation of salt, the supply of which was in each case a state monopoly. Unconsciously the municipality of Waadt supplied iodized salt, and so escaped goitre. The interpretation of this record is that both towns were exposed to the same low-grade infection, but that the supply of extra iodine to one section of the population enabled the thyroids of that section to deal with the infection without hypertrophy.

The more scientific experiments of McCarrison show how goitre follows feeding with fæcal material, and how a proper supply of iodine, vitamins, sun, and calcium reinforce the capacity of the thyroid to deal with the infection without enlargement.

Epidemic and endemic goitre are therefore not only important in themselves, but they provide the clue to the proper understanding of sporadic goitre. In the former a whole population is exposed to infection, in the latter an individual.

3. Sporadic Goitre.—Writers on endemic goitre recognize that even in goitre districts there are, as everywhere else, cases of sporadic goitre distinguishable from the prevailing type.

The following observations refer only to sporadic goitre, and the subject will be approached by a consideration of :—

1. The physiological enlargements of the thyroid.
2. The idiopathic diseases of the gland.
3. The symptomatic diseases of the gland.
4. The experimental production of goitre.
5. The role of infection in general in the production of goitre.
6. The part played by chronic syphilis.
7. A review of personal cases in the light of the above.

PHYSIOLOGICAL CHANGES IN THE THYROID GLAND

In the newborn, the gland is charged with maternal colloid. This disappears in a few days.

In childhood up to about 7 years, the structure of the vesicles is normal, and they are void of colloid.

Approaching puberty, there is an increase in the number of cells, but still no colloid.

In adult life, normal structure, normal trace of colloid.

After the menopause, colloid increases.

During pregnancy and menstruation there is increase in the size of the gland and increase in colloid.

The gland, therefore, can adapt itself to the requirements of the individual, and there seems to be a

relationship between the amount of colloid and the natural activity of the animal.

In health, power to return to normal after such a temporary adjustment is retained. The pathological border is crossed when the whole or part of the gland fails to return to normal.

IDIOPATHIC DISEASES OF THE THYROID

This group may be dismissed in a few words. Like any other gland the thyroid may be the primary seat of injuries, inflammations, and new growths, but cases in this group are rare. It is, however, difficult sometimes to distinguish clinically between a true simple adenoma and a solitary nodule secondary to past inflammation. The former is a new growth *sui generis*, the latter is the result of continued growth in gland tissue isolated by inflammatory fibrosis.

SYMPTOMATIC ENLARGEMENTS OF THE THYROID

1. The gland is an essential part of the mechanism of response to infection, and this will be more closely examined in another section.

2. The thyroid is an interacting endocrine gland. This is suggested by the sex distribution, enlargements in the female being eight times more frequent than in the male. The gland is also known to compensate for chronic adrenal exhaustion. Shock and worry cause first of all an outpouring and consumption of adrenaline. If the cause persists the slower acting thyroid compensates by increasing its

secretion, ultimately to produce clinical hyperthyroidism. This was demonstrated on a large scale during the Great War and is an important link in the correlation of chronic syphilis with disorders of the thyroid.

3. In overaction of the sympathetic system from any cause, we may expect hyperthyroidism. The sympathetic is the secretory nerve to the gland, and it is recognized that it may be difficult to decide whether hyperthyroidism is primarily due to thyroid or to sympathetic overaction.

The above-mentioned changes are normal physiological responses. The healthy thyroid retains the power to return to normal when the excitant is removed, but, as in the changes of puberty, so in this group the pathological border may be crossed when part or the whole of the gland fails to return to normal.

With regard to the foregoing, if we can discover a factor which causes either chronic adrenal deficiency or sympathetic overaction, we simultaneously discover an indirect cause of thyroid dysfunction. And if we find a single factor which may cause both adrenal deficiency and sympathetic disorders, such as chronic syphilis, that factor becomes important in the etiology of thyroid diseases. Its importance is not lessened by the fact that it is remediable.

EXPERIMENTAL PRODUCTION OF GOITRE

Breitner publishes the results of his experiments on dogs, and although it is difficult to interpret his

results correctly, and although they appear to have little bearing on the subject under discussion, they serve to maintain a sense of proportion and to remind us of the complexity of the problem.

In tabular form his records are :—

Experiment	Findings in one Week	Experiment Repeated but Iodine Administered afterwards
1. Normal dog. Hemithyroidectomy	Remainder enlarged. Increase in number of cells, but no colloid = parenchymatous type of adolescence and epidemics	Increased number of cells. Vesicles full of colloid = type of colloid goitre
2. Normal dog. Hemithyroidectomy with artificial stricture of trachea to lower basal metabolic rate (dog lies quiet in a corner)	Normal size. Tubes filled with colloid. After 6 weeks cells flat, colloid thick = atrophic colloid	Normal thyroid preserved
3. Normal dog. Hemithyroidectomy. Fixation abscess produced by intramuscular injection of turpentine	Increased number and size of cells. No colloid. The microscopical picture of Graves' disease, but not true Graves' disease	Colloid goitre produced

The interpretation seems to be that the thyroid function is in direct relationship to the activity of the animal. The element of infection does not enter into these experiments.

The difficulty comes in assessing the role of iodine. Breitner himself believes that iodine works against the dysfunction of the gland—always tending to restore it to normal. He says that pharmacologists have

proved: first, that iodine is the remedy for sympathetic hypertonus and therefore in this case tends to retain colloid in the thyroid; and secondly, that it is also the remedy for parasympathetic hypertonus. In the latter condition colloid is retained in the thyroid. Iodine breaks the hypertonus, the colloid is pushed into the circulation, and thus iodine in excess may convert a colloid goitre into a toxic goitre.

I have not been able to discover Breitner's authorities, nor been able to find any confirmation of his statements regarding the action of iodine on the autonomic nervous system. Opinion is not settled on the value of iodine in thyroid diseases, but I have given it for long periods without ill effect in those cases which I have believed to be syphilitic.

INFECTION AND GOITRE

Acute Infection.—Enlargement of the gland occurs in many infectious diseases. It has been reported in typhoid, scarlet fever, diphtheria, measles, cholera, influenza, acute rheumatism, acute infections of nasopharynx, erysipelas, puerperal fever (Osler and McCrae). I have noted it also in acute pulmonary phthisis and frequently in secondary syphilis. Whether the enlargement is a true thyroiditis, as suggested by Osler and McCrae, or a functional hypertrophy of an essential element of the defence mechanism, may be a matter of opinion, but one does not find corresponding enlargements in the testicle, another easily observed endocrine gland. Probably both elements play a part.

Chronic Infection.—The association between goitre and systemic infection must be inferred from the great number of symptoms associated with goitre. Osler and McCrae mention chorea, paralysis of muscles in neck, arm, hand, and leg, excessive sweating, dermatographia, urticaria, pruritus, ascites, vitiligo, scleroderma, alopecia, enlarged spleen. They also say that besides the lymph-glands near the thyroid, the bronchial and mesenteric glands as well as those in other parts of the body may be enlarged.

If the reader pauses for a moment to seek a common denominator for all the fore-mentioned conditions, he must at least agree that the ground is well prepared for a closer study of the relation between syphilis and goitre.

SYPHILIS AND GOITRE

" Tabes dorsalis is often a complication of goitre, and is of special interest from the possibility of a syphilitic origin of the thyroid alteration " (Osler and McCrae).

At least two authors have attempted to establish syphilis as a cause of goitre. Castex believes it to be the commonest cause of hyperthyroidism among the Argentinians. Engel-Reimers in a paper—said by Osler and McCrae to be the best on the subject—states that 50 per cent of early syphilitics have enlargement of the thyroid. The swelling begins early in the secondary stage ; it is soft, painless, and subsides slowly. Gummata on the other hand are rare.

When I wished to refer to this paper, I found there was no available copy in Great Britain, neither was there a translation into English. It was necessary to obtain a photostat from the library at Washington.

This disregard of syphilis by writers on goitre is illustrated in Joll's *Diseases of the Thyroid.* He dismisses syphilis in half a page, and then only refers to gummata. Either he is unaware of the changes in secondary syphilis, or disagrees with the views of Engel-Reimers. But if it can be shown that a common chronic disease, syphilis, affects the thyroid of about one-half of its victims in the early stages, and if we accept the axiom that, e.g., nodular goitre and secondary Graves' disease are late forms but essentially the same disease as parenchymatous goitre and due to the same stimulus, then it is necessary to think of syphilis in any chronic disorder of the thyroid. Further, since 90 per cent of carcinomata of the thyroid arise in chronic nodular goitre, to discover and remove the cause of the latter is to prevent the development of the former.

The point of view of Joll and the writer is essentially different. The first, by writing a large work on a small gland, accepts Virchow's attitude that the body and personality are but the vehicle of a diseased gland. The main remedy for all disorders of the gland is surgical removal. The second or general practitioner's view is concentrated on the person, and goitre is only one sign in an ailing organism, and one which only exceptionally calls for direct treatment. Any associated conditions are therefore more likely to

impress the family doctor than the surgeon, whose chief concern is whether a given goitre requires removal or not, and this may account for the omission to give syphilis its proper place in the text-books.

In the subsequent list of cases all enlargements of the thyroid are included, and from the associated conditions an estimate is made of the part to be allotted to syphilis in the etiology.

SUMMARY OF AUTHOR'S CASES OF GOITRE

Group	Idiopathic	Associated with Infection	Associated with Syphilis	Associated with doubtful Syphilis	Total
I. Hyperthyroidism without enlargement of gland ..	30	20	3	11	64
II. Hyperthyroidism with simple enlargement of gland	16	16	3	7	42
III. Hyperthyroidism with adenoma (or single nodule) ..	6	7	4	6	23
IV. Adenoma (or single nodule) without hyperthyroidism	6	11	2	16	35
V. Nodular goitre ..	—	13	3	3	19
VI. Toxic goitre ..	—	5	3	1	9
VII. Myxœdema ..	—	—	—	4	4
Totals ..	58	72	18	48	196

To recapitulate: the facts which entitle syphilis to special significance in this matter are:—

1. It is a chronic lifelong infection which affects the thyroid in about half the cases in the secondary stage.

2. By the regular production of a chronic paravertebral lymphadenitis in the latent stage, it is an irritant of the autonomic nervous system, and can thus produce hyperthyroidism.

3. By regularly attacking the adrenal body in the female, it is a cause of chronic adrenal subfunction, which is naturally compensated by thyroid hyperfunction, a fact which satisfactorily accounts for the prevalence of goitre in women. Because of its importance in this connection and the neglect it has suffered, Engel-Reimers' article on the subject is reproduced in Chapter III.

The term adenoma is applied to single nodules. I believe these are most often single nodules of parenchymatous goitre, and not true simple new growths in a normal gland as the term 'adenoma' suggests.

The term ' doubtful syphilis ' is applied to those cases which do not reach the diagnostic standards demanded by orthodox teaching, namely: positive Wassermann; pathognomonic signs; demonstration of spirochætes. These standards have already been criticized.

A paper based on experience in general practice must necessarily concern itself with ' doubtful ' cases of syphilis, because these outnumber greatly cases clearly in the tertiary stage of the disease.

The associated symptoms and responses of the individual (not necessarily the goitre) to the therapeutic test satisfy me that these cases are examples of latent syphilis, and while it is not possible to satisfy exact scientific tests, one can remember the saying that nine-tenths of the things we *know* in medicine are a matter of faith in human testimony—we have not verified them for ourselves. Experience,

on the other hand, is a more formless but truer knowledge of what we have verified for ourselves.

Clinical outlines of the 'doubtful' and syphilitic cases follow. The idiopathic and infection cases are not included.

The whole series teaches that a patient presenting signs of thyroid dysfunction must be investigated for an associated infection, and pathology, logic, and experience combine to demand that chronic syphilis be consciously excluded before resorting to purely symptomatic treatment.

Group I.—HYPERTHYROIDISM* WITHOUT ENLARGEMENT OF GLAND

SEX	AGE	OCCUPATION	LEADING SYMPTOM	ASSOCIATED SYMPTOMS
A. **With Syphilis.**—				
M.	24	Railway worker	Tremor	W.R. +. Sank into asthenic state and died. Diagnosis: acute cerebral syphilis
M.	35	Clerk	Afraid of everything	Musical systolic bruit all over heart. Reflexes +. W.R., 2 M.H.D. Dusky injection of tonsils. Pruritus and eczema 5 years. Wife had old interstitial keratitis; no pregnancy.
M.	30	Quarryman	Sore throat	W.R. + +.
B. **Syphilis Doubtful.**—				
M.	49	Cleric	Nasolaryngeal catarrh	History of ulcer of leg and generalized rash. Wife "a chronic abdomen": several laparotomies. No children. A chronic invalid relieved by specific therapy

* 'Hyperthyroidism' = tremor, *tachycardia*, moist skin.

Group I.—HYPERTHYROIDISM WITHOUT ENLARGEMENT OF GLAND—*continued.*

SEX	AGE	OCCUPATION	LEADING SYMPTOM	ASSOCIATED SYMPTOMS
F.	35	Teacher	Sore tongue (plicate type)	Flatulent indigestion. Mother has perforated septum, angina pectoris, and chronic indigestion. All symptoms relieved by specific treatment
F.	32	Book-keeper	R. hypochondrial pain	Perihepatitis, plicated tongue, chronic rheumatism with low pyrexia. Therapeutic test positive
F.	34	Housewife	Increasing catarrhal deafness	Chronic rheumatism. Palpitation. B.P. 170/100. Father is master mariner. Mother diabetic. Husband symptom-free, but his father and grandmother have perforations of nasal septa and other signs. Therapeutic response good
F.	43	Nurse	Chronic abdominal pain	Laparotomy and X rays at teaching hospital without relief. Tender aorta. Unequal pupils. All relieved by specific treatment
F.	20	At home	Chronic naso-pharyngeal catarrh	Mother has typical Hutchinson teeth
F.	30	At home	Chronic naso-pharyngeal catarrh	Middle-ear deafness and scarred drums. Daughter of a sailor. Therapeutic response + +.
F.	50	Cook	Dysphagia and anæmia	Fibrotic tongue, Aortic regurgitation. W.R. in C.S.F., 2 M.H.D. (weakly positive)
F.	34	At home	Chronic abdominal pain	(Daughter of innkeeper). Star-shaped scars on liver seen at appendicectomy. Therapeutic response good

Group I.—HYPERTHYROIDISM WITHOUT ENLARGEMENT OF GLAND—*continued*

SEX	AGE	OCCUPATION	LEADING SYMPTOM	ASSOCIATED SYMPTOMS
B. **Syphilis Doubtful,** *continued.*—				
M.	40	Shop assistant	Chronic bullous rash on ulnar border of palms	Unequal pupils. Throat red, with sticky frothy mucus, but no discomfort. Therapeutic response good. Brother has aortic regurgitation and asthma
M.	29	Clerk	Nervous	Father fell dead in street. Mother an invalid (multiple signs consistent with chronic syphilis; W.R. negative; history of six miscarriages). Two sisters have hyperthyroidism. Two sisters have symptomless enlargements of thyroid. Remaining brother a psychotic unfit for work

Comment.—Out of the 11 doubtful syphilitics, I regard 7 as congenital. In 4 of these, chronic nasopharyngeal catarrh was a feature and was relieved by specific treatment. The leading symptom throughout this group was relieved by a combination of mercury, iodides, and bismuth. Arsenicals of the 606 type are reserved for W.R. positive cases.

Group II.—HYPERTHYROIDISM WITH ENLARGEMENT OF GLAND

SEX	AGE	OCCUPATION	LEADING SYMPTOM	ASSOCIATED SYMPTOMS
A. **With Syphilis.**—				
F.	65	Housewife	Ataxia	B.P. 260/160. W.R. +. Gumma of abdominal wall 20 years ago

Group II.—HYPERTHYROIDISM WITH ENLARGEMENT OF GLAND—*continued*

SEX	AGE	OCCUPATION	LEADING SYMPTOM	ASSOCIATED SYMPTOMS
F.	17½	Domestic	Eczema of face, neck, and flexor aspect of elbows	W.R. + +.
F.	21	At home	Dysphagia	Precordial pain. W.R. +.
B. **Syphilis Doubtful.—**				
M.	28	Chauffeur	Angioneurotic œdema	Plicated tongue, unequal pupils, enlarged epitrochlear glands. Therapeutic test positive
M.	40	Butcher	Pain in chest	Chronic rheumatism. 100 per cent war pension for myocarditis. Epitrochlears +. Therapeutic response good
F.	45	Domestic	Chronic myalgia and abdominal pain	One of 3 sisters, 1 similarly affected and relieved by mercury and iodides. 1 died of exophthalmic goitre
M.	36	Joiner	Pain round chest	Excessive sweating. Blood W.R., 1 M.H.D. C.S.F., 0·5/1000 protein. Wife rheumatic; no pregnancy. Both relieved by iodides and mercury
F.	45	Housewife	Chronic abdominal pain	Nervous dysphagia, varicose veins, laryngitis, cancerphobia. Good response to treatment. Hepatitis in husband cured by iodides
F.	31	Housewife	Hypochondriac	Anæmic. Only child of sailor. Therapeutic response good
F.	36	Barmaid	Alcoholic neuritis	W.R., 1 M.H.D. Mother has A.R. pupils. Father, brother, and sister died of alcoholism. Remaining sister has parenchymatous goitre.

Comment.—In this group also dystrophy of the thyroid combined with signs in other parts of the body led to a diagnosis of syphilis and relief by treatment. In two of the W.R. + cases the leading symptoms appeared at first to have no connection with this disease—but the rule to assume the presence of chronic infection and to exclude syphilis by direct examination prevented error.

Group III.—SINGLE NODULE OR ADENOMA WITH HYPERTHYROIDISM

SEX	AGE	OCCUPATION	LEADING SYMPTOM	ASSOCIATED SYMPTOMS
A. **With Syphilis.**—				
F.	20	At home	No complaint	Typical congenital stigmata.
F.	42	Housewife	Chronic rheumatism	Fibrotic tongue. Secondary glaucoma after iridocyclitis. Four miscarriages. No children. Father died of creeping paralysis. Mother fell down dead
F.	53	Housewife	Pain in breast 7 or 8 years	Chronic pharyngeal catarrh Sudden shooting pains in head. Paræsthesia (sense of heat between skin and flesh); both ulnar nerves insensitive. W.R. + +.
F.	32	Housewife	Asthma 4 mth., attributed to a motor accident	W.R. +. Only child died at 6 weeks of marasmus, snuffling, general desquamation
B. **Syphilis Doubtful.**—				
F.	34	Housewife	No complaint	Tongue has smooth pale sides. Unequal reacting pupils. Hazy cornea—present in brother and sister also. Husband has granuloma of arm and W.R. +.

Group III.—SINGLE NODULE OR ADENOMA WITH HYPERTHYROIDISM—*continued*

SEX	AGE	OCCUPATION	LEADING SYMPTOM	ASSOCIATED SYMPTOMS
F.	51	Housewife	Pain in left side of chest and down left arm	Rheumatic pains back and joints. Pupils unequal. No reaction to light, sluggish to accommodation. Both epitrochlear glands enlarged
F.	55	Cook	Anæmia dysphagia	Arrhythmia with paroxysms of tachycardia and orthopnœa, albuminuria, polyarticular rheumatism. Dry red glazed frothy throat. Best therapeutic response was to specific treatment
F.	55	Retired Teacher	Cardiac arrhythmia	B.P. 145/80, P. 120. Polyarticular rheumatism. Unequal reacting pupils. Good therapeutic response. Two daughters, both of whom have parenchymatous goitre. Only son had crepitations in root of lung for several months, low pyrexia, sputum negative to T.B. Recovered after Bismostab
F.	35	At home	Long history of gastric pain	Mother is stone deaf and has trigeminal neuralgia. Father chronic bronchitis. Both respond well to mercury and iodides
F.	31	At home	Pain behind manubrium sterni on swallowing	Grandmother, mother, and only surviving aunt have chronic iridocyclitis. Aunt is totally blind from this cause, and a typical congenital syphilitic

Comment.—A localized lump in the thyroid is evidence that the dystrophy is of longer standing than in the simple enlargement of *Group II.* For

this reason the concurrent signs in the syphilitics are better marked, and the proportion of cases recognizable as syphilitic rises—in this short series to 10/23.

Group IV.—SINGLE NODULE OR ADENOMA WITHOUT HYPERTHYROIDISM

SEX	AGE	OCCUPATION	LEADING SYMPTOM	ASSOCIATED SYMPTOMS
A. **With Syphilis.—**				
F.	72	Housewife	Clinically 'carcinoma' of stomach	W.R.+. Recovered under iodide. Was asthmatic 12 years
F.	51	Housewife	Shaky and despondent	Discomfort in precordium and left arm. Pupils unequal; no reaction to light, sluggish to accommodation. Epitrochlear glands both enlarged. No children
B. **Syphilis Doubtful.—**				
F.	60	Spinster	"Nerves"	B.P. 170/90. Epitrochlear glands enlarged. Old iritis with synechiæ and immobile left pupil
F.	65	Spinster	Chronic rheumatism in hands and legs	Plicate tongue, unequal pupils. Sister of preceding case. Only 2 survivors of 10 children. Several died of strokes. Auricular fibrillation. Therapeutic response of general condition satisfactory in both
M.	58	Joiner	Chronic headache	Abdominal pain, old hydrocephalus, epitrochlear glands enlarged. Slowly increasing catarrhal deafness. Old iritis and secondary glaucoma one eye. Pancreatic insufficiency. Therapeutic response good.

Group IV.—SINGLE NODULE OR ADENOMA WITHOUT HYPERTHYROIDISM—*continued*

SEX	AGE	OCCUPATION	LEADING SYMPTOM	ASSOCIATED SYMPTOMS
F.	40	Housewife	Chronic mastitis of both breasts	Unequal reacting pupils. Rough finger-nails. Had catarrh and asthma for several years. Cured by vaccine
F.	22	Housewife	Giant urticaria 15 months	Had resisted all treatment. Father an asthmatic mariner. Mother a chronic asthmatic. Patient is youngest of 3 survivors of 14 children. All the others died in infancy. Therapeutic response dramatic and permanent
F.	60	Housewife	Discomfort in throat	Husband died of locomotor ataxia. One child, no miscarriage. Left thumb-nail has no cuticle, skin edge is chronically swollen and rough
F.	55	Teacher	Loss of voice	Chronic nasopharyngeal catarrh. Pallor, wasting, and premature senility. Therapeutic test positive and lasting
F.	46	Housewife	Trigeminal neuralgia	L. external rectus palsy. Middle ear deafness L. W.R. negative, but recovered on mercury and iodides
F.	38	Housewife	Chronic abdominal pain	Spastic colon. Cancerphobe. Tachycardia and arrhythmia. B.P. : R. radial 110/95 ; L. radial 140/95. Two miscarriages, two children lost in infancy. One of three survivors aged 12 has adenoma of thyroid. Has been relieved by specific treatment several times during the past 10 years

Group IV.—SINGLE NODULE OR ADENOMA WITHOUT HYPERTHYROIDISM—*continued*

SEX	AGE	OCCUPATION	LEADING SYMPTOM	ASSOCIATED SYMPTOMS
B. **Syphilis Doubtful,** *continued.*—				
F.	52	Housewife	Dysphagia from hard ulcerating mass in upper œsophagus	Cured by mercury and iodides
F.	36	Housewife	Pain in precordium and down left arm	Mother was syphilitic. Patient reacted to treatment.
M.	27	Quarryman	Intermittent precordial pain spreading down both arms	Glands post. triangles of neck. Recovered with Hg and KI after failure of symptomatic treatment
F.	36	Maid-servant	Intermittent claudication in legs	Spastic dysphagia. Asthmatic as a child and has had mucous colitis. Both parents died of malignant disease. Therapeutic test positive after 2 years' failure of symptomatic treatment
F.	54	At home	Anæmia	Some fibrosis of tongue. Father was congenital syphilitic. One sister has diabetes, another has vitreous floaters. All do well on mercury and iodides
F.	42	Housewife	Ulceration of upper end of œsophagus, with dysphagia one month	Cured by mercury, iodides, and bismuth

Comment.—As in *Group III* approximately half of these patients fall into the syphilitic sections. In no case was direct complaint made of the thyroid. Together, *Groups II* and *III* form the strongest

support of the writer's hypothesis that a localized enlargement of the thyroid is evidence of systemic infection. In many cases this is either quiescent or completely overcome ; in others associated signs such as epitrochlear glands, smooth or plicate tongue, unequal pupils, rough finger-nails, etc., indicate the nature of the chronic infection, and the physician must take this into account before he attempts to deal with the symptom for which the patient seeks relief.

Group V.—NODULAR GOITRE

SEX	AGE	OCCUPATION	LEADING SYMPTOM	ASSOCIATED SYMPTOMS
A. **With Syphilis.—**				
F.	60	Housewife	Chronic ulcers of bladder	Gumma of leg. Heart-beat irregular, rapid, forcible. Spleen enlarged. Crepitations base L. lung. W.R. +
F.	54	Farmer's wife	Precordial pain	Auricular fibrillation. Pupils unequal, reacting. Kept in bed for six months. Only sister has large nodular goitre, and this sister's husband has tabes dorsalis. Patient improved on rest with mercury and iodides. Four years later left pupil had become of Argyll-Robertson type. At present, 9 years after first note, she is still doing housework and light dairying.
F.	40	At home	Chronic intractable headache	Epigastric pain and vomiting. Choroiditis and optic atrophy. W.R. +. Brother is typical congenital syphilitic. Alive and doing housework 12 years later

Group V.—NODULAR GOITRE—*continued*

SEX	AGE	OCCUPATION	LEADING SYMPTOM	ASSOCIATED SYMPTOMS
B. **Syphilis Doubtful.**—				
F.	45	Housewife	Flatulent indigestion	Lack of concentration, and loss of memory. Primary glaucoma. Ptosis of R. lid came on when she was 25. Opaque ear-drums. Leaden feeling in precordium and down left arm. Relieved by mercury and iodides for 3 years. Only child. Mother had carcinoma uteri, chronic rheumatism, auricular fibrillation, arterio-sclerosis with retinal hæmorrhages
F.	65	Housewife	Chronic rheumatism in hands and legs	Unequal reacting pupils. Hypertrophic (plicate) tongue. Auricular fibrillation controlled by digitalis. Found dead in bed
F.	46	Farm helper	Nerve deafness	Tic of head, headaches, anæmia. Burning pain in epigastrium. Moderate therapeutic response. Mother and only sister have nodular goitres

Comment.—The therapeutic response in this group is not as satisfactory as in the former, though no case has been made toxic by iodides. Treatment has been principally symptomatic—attacking the syphilis with small dosage over long periods.

Group VI.—Toxic Goitre

Sex	Age	Occupation	Leading and Associated Symptoms
A. **Primary. Non-Syphilitic.**—			
F.	21	Teacher	Chronic mastitis. Rapid course. Died
F.	56	Housewife	Cured by thyroidectomy
F.	34	Housewife	Cured by rest and appendicectomy
B. **Primary. Syphilitic.**—			
F.	52	Housewife	Cured by thyroidectomy. W.R. +.
F.	49	Farmer's wife	Cured by specific treatment and rest. W.R. +.
C. **Secondary. Non-Syphilitic.** —			
F.	42	Housewife	Bilateral renal calculus and pyuria for 7 years. Died of cardiac failure
F.	62	Farmer's wife	Died of cardiac failure
D. **Secondary. Syphilitic.**—			
M.	47	Quarryman	W.R. +. Improved to working capacity by specific treatment. Died of carcinoma of stomach 8 years later
E. **Syphilis Doubtful.**—			
F.	69	Spinster	Illness terminated fatally with cardiac failure. Features were persistent tachycardia with severe precordial pain. Brother: W.R. +, miotic A.R. pupils. Had a small chancre in youth. No secondary or other tertiary signs. 1 sister died from pulmonary phthisis. 1 sister blind from retinitis pigmentosa, with nerve deafness, also has adenoma of thyroid. Whole family is regarded as congenital

Comment.—This group is small, but illustrates well a point which the writer seeks to emphasize. By a coincidence the two syphilitic primary Graves'

disease came under observation at the same time. Both were known to be syphilitic before the onset of thyroid disease; at first the two conditions were not associated. Both were advised to undergo operation at the hands of one of the leading surgeons in this specialty. One consented, underwent operation, and recovered. The other refused operation, continued treatment with mercury and iodides, and recovered in a slightly longer time. Now, ten years later, both are well and working. Spontaneous recovery from Graves' disease is well known, and may have occurred in the second case. I do not wish to suggest any other treatment than thyroidectomy in toxic goitre—even in the true syphilitic case this is the most certain and rapid cure; but I venture to protest against the attitude of those surgeons who disregard the syphilis when they remove glands from syphilitics. It has happened twice in my own experience, and is to be expected when syphilis is scarcely mentioned in the leading British text-book (Joll). The case of secondary Graves' disease in a syphilitic shows that specific treatment can be valuable in this condition.

Group VII.—MYXŒDEMA

SEX	AGE	OCCUPATION	LEADING AND ASSOCIATED SYMPTOMS
Syphilis Doubtful.—			
F.	60	Housekeeper	Loss of hair. Temporary insanity 10 years ago. Two brothers alive and well; 1 brother died of cancer aged 44; 1 sister died of cancer aged 40; 1 sister is asthmatic; 1 sister has a white leg.

Group VII.—MYXŒDEMA—*continued*

SEX	AGE	OCCUPATION	LEADING AND ASSOCIATED SYMPTOMS
F.	68	Cook	1926. Loss of hair and eyebrows. Chronic bronchial catarrh. Relieved by thyroid and iodine 1927. Large ovarian cyst removed. Transient failure of vision (spasmodic). B.P. 180/80. 1929. Carcinoma of rectum. After operation she developed complete arrhythmia with aortic insufficiency. Heart enlarged. B.P. 120/30. Died of secondary deposits in liver, 1930. P.M.; Localized small lymphocytic infiltrations in heart, pancreas, and adrenal
F.	38	Housewife	1927. Amenorrhœa. Hot flushes, headaches, sleepless, painful dry swallow, occasional vertigo 1932. Giant urticaria. Married at 34. No children. 1 miscarriage at two months. *Family History.*—Father died of an ascending paralysis, in bed four years. Mother died of repeated strokes. 3 brothers and sisters died in early infancy; 1 died of convulsions at 8 months; 1 died at 12, St. Vitus and enlarged heart; 1 died of phthisis at 24. X rays showed transverse diameter of heart increased by one-half and prominent aortic shadow. 1 brother is inmate of asylum. 1 sister unknown to me said to be the subject of chronic headaches. 2 sisters alive, chronic minor complaints have been relieved by mercury and iodides after failure of symptomatic treatment
F.	38	At home	W.R. +. Choroiditis. Sudden cardiac death six years later

Comment.—A small group, the details of which make it evident that the thyroid atrophy was not the primary disease. In one, evidence of syphilis is conclusive; in two others circumstantial evidence from family history and therapeutic response is strong.

CHAPTER III

ENLARGEMENT OF THE THYROID IN EARLY SYPHILIS

(*Translated from Engel-Reimers**)

As is known, the first constitutional effects of syphilis usually become noticeable at the time of cicatrization of the primary lesion. If, until then, the toxin has produced only local changes at its point of entry and in the neighbouring lymph-glands, there now set in important disturbances in the general condition. Changes in the appearance of the patient set in, associated with changes in temperature, gastric disturbances, neuralgic and rheumatoid pains, and towards the end of the so-called second period of incubation the well-known picture of syphilitic chlorosis develops, followed immediately by the early eruptions on the skin and visible mucous membranes.

Since it is known that this chlorosis is always accompanied by a distinct increase in the white blood-cells it seemed natural to inquire whether the leucocytosis is due merely to a general swelling of the lymph-glands or whether other blood-forming organs show changes during this period. It was, in

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* J. ENGEL-REIMERS, *Jahrb. d. Hamburg. Staattskrankenanst*, 1891–92, iii, 430–436.

fact, found that shortly before the onset of the first cutaneous eruption there is occasionally an appreciable enlargement of the spleen, and it is not improbable that some of the osteocopic pains, especially sternalgia, are not, as is generally believed, due to periostitis, but are attributable to changes in the bone-marrow; in fact, that it is perhaps similar to the sternal pain occurring in myelogenous leukæmia.* These considerations led me to test systematically the behaviour of the thyroid gland in early syphilis, since this organ is certainly of great importance in the chemistry of the blood.

Especially marked enlargement of the thyroid in some cases of early syphilis has not escaped the notice of French observers. Mauriac, after describing the enlargement of the spleen and the hypertrophy of the tonsils, which, like the swelling of the follicular glands at the base of the tongue and of the pharynx, are often enough found before the appearance of the papules in the mouth, says: "J'ai constaté aussi parfois la tuméfaction de la glande thyréoide tout à fait au début de la syphilis. Dans un cas, dont j'ai été témoin, il survint un véritable goitre syphilitique, qui dura plusieurs semaines et fut assez volumineux pour comprimer la trachée et le larynx et produire un peu de gêne de la respiration et de raucité dans la voix" (*Syphilis primitive et Syphilis secondaire*, 1890,

* In cases of early syphilitic chlorosis with pronounced osteocopic pain, our researches have always revealed a large number of eosinophilic leucocytes in the blood. A detailed report of this will shortly be published elsewhere.

p. 474), and Jullien also seems to speak from personal experience when he says: "Le corps thyréoide échappe le plus souvent au processus, mais il est bien avéré, qu'il présente parfois une tuméfaction temporaire des plus accusées" (*Traité pratique des Maladies vénériennes*, p. 642).

Investigations in this hospital have, however, shown that enlargement of the thyroid in early syphilis is by no means a rare, exceptional occurrence, but rather is encountered very frequently—on an average in about half of all cases. In 152 women attacked by the first general symptoms of the disease we observed it 86 times, and in the early stages in 98 men 44 times, that is in 56 per cent and 45 per cent respectively of the cases examined for this condition. In 20 men (20·4 per cent) and 52 women (34 per cent) there was a moderate struma, visible from a distance; in the others only the lateral lobes were enlarged, while the central lobes were not affected. The swelling was always soft and painless, and did not trouble the patients in any way, and had not even been noticed by most of them before our examination.

Naturally, pregnant and nursing women,* and all individuals from goitrous districts, were excluded. In spite of this, after excluding all doubtful cases, the question to be discussed in the first place remains: Is the thyroid enlargement really due to syphilis

* "Swelling of the thyroid due to pregnancy must be regarded as almost a constant finding. During lactation it is also very frequent" (FREUND, "Die Beziehungen der Schilddruse zu den weiblichen Geschlechtsorganen," *Deut. Zeits. f. Chir.*, xviii, 254.)

alone, or may it not also be dependent on other influences, especially on the habitual sexual stimulation in prostitutes? It is, of course, well known that the thyroid gland in women is closely connected with the sexual organs—even in antiquity an increase in the circumference of the neck on the day after marriage was regarded as a sure sign of defloration,* and frequent sexual stimulation is regarded by many observers as a factor favouring the development of endemic goitre.†

As regards this question, the fact must first be emphasized that thyroid enlargement is to be found just as often in women who have contracted syphilis as the result of a single indiscretion as in professional prostitutes. In 74 early syphilitic individuals of the first category we found it 42 times (= 56 per cent) including 18 visible goitres (= 24 per cent), and in 78 persons of the second group it was found 44 times (= 56 per cent) including 34 slight goitres (= 43 per cent).

Then the fact must be considered that the frequency of this change in men is only slightly less than in women, and finally, that repeated comparative measurements constantly showed a slightly greater circumference of the neck in men with early syphilis than in those with gonorrhœa or ulcus molle.‡ To

* "Non illam nutrix orienti luce revisens Hesterno collum poterit circumdare filo." (CATULLUS, *Carmen* 64, 377.)

† FREUND, *loc. cit.*, p. 223.

‡ In the women's department such comparative measurements could not be carried out, as there are always very few non-syphilitic women there.

exemplify this I give here the results of a series of measurements undertaken on Nov. 4, 1893 (*see Table I*, p. 50). In 22 men with early syphilis the maximum circumference of the neck was 40 cm., the minimum 36 cm., and the average 37·5 cm. In 22 men with gonorrhœa the corresponding sizes were 36, 32, and 34 cm. Among the 22 men with syphilis 10 had a distinct enlargement of the thyroid, whereas this was found in only one of those with gonorrhœa, with a neck circumference of 36 cm. The conclusion that the unusually frequent thyroid enlargement of early syphilis is not a complication due to other causes, but a direct result of syphilis, is therefore justified.

So far as my experience goes, the swelling generally occurs very early, during the second period of incubation, or with the first outbreak of constitutional symptoms. It does not appear to be influenced directly by antisyphilitic treatment, but, like the swelling of the lymph-glands, it regresses very slowly in the course of a few years, and finally does not increase when later relapses occur. My investigations on this last point, which require measurements spread over many years, are not yet complete, and I propose to report on them later, on the basis of larger series of figures.* In prostitutes, in whom there is the additional effect of sexual over-excitement, the enlargement often definitely persists for the rest of their lives. Lancereaux has already remarked: " Le

* As far as can be ascertained this paper was never published.

corps thyréoide est fréquemment volumineux chez les femmes, qui sont affectées de syphilis ancienne."*

As a rule the early syphilitic enlargement of the thyroid causes no symptoms whatever, as has been said above. In this respect it is similar to the acute epidemic goitre which occasionally occurs in garrisons, and which, as Lebert definitely states,† does not, as a rule, cause any other disturbances. The possibility is, however, not excluded that in rare cases it may lead to more severe diseases of the organ and to myxœdema. Kohler,‡ at any rate, reports on a syphilitic woman, aged 50 years, who showed the characteristic symptoms of myxœdema, and was completely cured of them by antisyphilitic treatment. Symptoms of Basedow's disease do not appear to be associated with this condition. Among 30 men with thyroid enlargement there was only one (with a distinctly visible struma and a neck circumference of 40 cm.) who showed a quite slight protrusion of the right eyeball, a suggestion of Graefe's sign, and pulsation of the carotids, and among 25 carefully examined women with early syphilitic goitres there was also a completely negative result, with one possible exception. In spite of this a detailed report of the results of this investigation is probably not entirely without interest, as it shows how extraordinarily frequently nervous disturbances (especially hypalgesias and increased tendon reflexes) can be

* *Traité historique et pratique de la Syphilis*, p. 277.

† *Die Krankheiten der Schilddrüse*, p. 96.

‡ *Deut. med. Woch.*, 1892, p. 122.

found in women with early syphilis, when careful tests are made.

As a matter of fact, as I should like to remark in conclusion, syphilis is not the only infectious disease which affects the thyroid. R. Demme observed acute enlargement of the thyroid in many cases in an epidemic of measles,* and Holz has described the occurrence of acute thyroiditis in influenza.†

Table I.—Circumference of Neck in Men in Early Syphilis and Gonorrhœa

Early Syphilis			Gonorrhœa		
	cm.			cm.	
H	37		R	35	
B	37		S	33	
S	39	Enlarged lateral lobes	B	34	
L	36		T	34	
K	37		N	34	
B	38	Enlarged lateral lobes	C	33	
S	40	Struma	S	33	
J	36		B	33	
R	38	Enlarged lateral lobes	H	34	
B	38		B	33	
A	37		B	34	
S	39	Enlarged lateral lobes	V	32	
V	39	Enlarged lateral lobes	D	34	
S	37		S	32	
W	37		S	34	
K	37		K	35	
M	38		S	35	
H	39	Enlarged lateral lobes	P	32	
R	40	Struma	N	33	
L	38		K	36	Enlarged lateral lobes
W	39	Enlarged lateral lobes	R	34	
R	40	Struma	T	34	

* *Schmidts Jahrb.*, 1883, ii, p. 110.

† *Berl. klin. Woch.*, 1890, No. 4.

Table II.—THYROID MANIFESTATIONS IN EARLY SYPHILIS

No.	Struma	Circumference of Neck	Exophthalmos	Palpitation	Pulse	Tendency to Perspire	Graefe's Sign	Stellwag's Sign	Möbius's Sign	Tremor	Sensibility	Reflexes	Pupils
		cm.											
1	Distinct	35·5	0	0	80	0	0	0	0	0	Normal	Lively	Normal
2	Distinct	37·5	0	0	96	0	0	0	0	Slight tremor of hands and tongue	Normal	Lively	Normal
3	Distinct	35	0	0	112	0	0	0	0	Slight tremor of hands and tongue	Normal	Lively	Normal
4	Slight	34	0	0	100	0	0	0	0	0	Normal	Normal	Normal
5	Distinct	33·5	0	0	88	0	0	0	0	0	Normal	Increased	Normal
6	Distinct	34	0	0	80	0	0	0	0	0	Normal	Normal	Normal
7	Distinct	35	0	0	112	0	0	0	0	0	Hypalgesia in both upper arms and on back to middle line	Normal	Normal
8	Slight	31·5	0	Present, systolic murmur at apex	110	Present, especially on hands	0	0	Insufficiency of right internus	Present	Normal	Much increased	Normal

Table II.—THYROID MANIFESTATIONS IN EARLY SYPHILIS—*continued*

No.	Struma	Circumference of Neck	Exophthalmos	Palpitation	Pulse	Tendency to Perspire	Graefe's Sign	Stellwag's Sign	Möbius's Sign	Tremor	Sensibility	Reflexes	Pupils
		cm.											
9	Slight	32	o	o	80	o	o	o	o	o	General diminution of pain sensation except on soles of feet. Touch normal	Increased	Normal
10	Slight	31·7	o	o	100	o	o	o	o	o	Diminished	Very lively	Normal
11	Distinct	34	o	o	92	Present	o	o	Insufficiency of left internus	o o	Hypalgesia in back, chest and arms	Increased	Normal
12	Very distinct	34	o	o	112	o	o	o	Insufficiency of both interni	o	Normal	Weak	Normal
13	Very distinct	34	Left eyeball prominent	o	100	o	o	o	o	o	Normal	Increased	Normal
14	Distinct	33·5	o	o	86	o	o	o	Slight insufficiency of both interni	o	General hypalgesia	Lively	Normal
15	Distinct	34	o	o	90	Present	o	o	Slight insufficiency of the interni	o	Pronounced general hypalgesia	Tendon reflexes normal: skin reflexes weak	Sluggish

16	Distinct	33	0	0	84	0	0	0	Insufficiency of both interni	0	Slight sensory disturbances	Lively	Normal
17	Slight	33·5	0	0	100	0	0	0	Insufficiency of both interni	0	Slight sensory disturbance	Very lively	Normal
18	Distinct	34 (very thin)	0	0	116	0	0	0	0	Slight tremor of hands	Slight sensory disturbance	Very lively	Normal
19	Slight	32	0	0	80	0	0	0	0	0	Slight sensory disturbance	Lively	Normal
20	Very distinct	37	0	0	116	Present (no suggested diarrhœa)	±	0	Insufficiency of the interni	0	Slight sensory disturbance	Very lively	Left pupil enlarged
21	Slight	29·5	0	0	120	0	0	0	Insufficiency of left internus	0	Normal	Lively	Normal
22	Distinct	32·5	0	0	84	0	0	0	Slight nystagmus in extreme positions	0	Diminished	Lively	Normal
23	Distinct	32	0	0	96	0	0	0	0	0	Normal	Normal	Normal
24	Slight	32	0	0	116	0	0	0	0	0	Diminished	Lively	Normal
25	Very distinct	37	0	0	76	0	0	0	0	0	Total analgesia on whole body except face	Tendon reflexes increased, skin reflexes absent	Normal

CHAPTER IV

ALLERGY

THE clinical states discussed in this and the next two chapters are usually called allergic. One of the present objects is to suggest that a group name such as ' disturbances of the autonomic nervous system ' would be more likely to lead to the discovery of the basic cause. Allergy has been defined as comprising many clinical conditions showing one common etiological characteristic—namely, hypersensitiveness to proteins or other substances which are innocuous to normal people. It is agreed that only an autonomic nervous disturbance can explain the sudden local manifestations in asthma, angioneurotic œdema, etc.

In all the papers on the subject which the writer has been able to read, the accent is on the exciting cause—pollen, etc.—and on the receptor organ—nasal mucous membrane, etc. The name toxic idiopathies itself lays stress on the poison rather than on the unstable autonomic system which reacts to one or several subliminal stimuli. Victims of these states are said to be allergics, and treatment is directed to : (*a*) Remove the cause ; (*b*) Desensitize the patient with increasing doses of the irritant.

CONDITIONS ASSOCIATED WITH ALLERGY

Let us for a moment pass in review some of the features which are known by experience to be associated with the allergic state, namely: (1) Heredity; (2) Intestinal disorders; (3) The psychological element; (4) Endocrine disorders.

Heredity.—Heredity is known to play an important part, and it is true that a sensitive autonomic system may be as truly inherited as is syndactyly or such inborn error of metabolism as alkaptonuria. Hypochlorhydria, deficiencies of liver action, and defects of protein metabolism are named as possible hereditary features bearing on the problem of allergy. It is, however, likely that this group is numerically small.

I have failed to find any reference to a disease which is certainly transmitted to a second and probably to a third generation, which commonly affects the liver, and only a little less frequently the pancreas. Lapage, however, describes a proneness to catarrh and glandular enlargements in his allergic patients, which he attributes to a lowered resistance to infection consequent on overloading of metabolism. At this point one may recollect that a traditional remedy for the catarrhal child is grey powder, and for general adenitis is the syrup of iodide of iron, and defer more detailed consideration to another page.

Intestinal Disorders (particularly spastic colon and colitis).—The sequence of events here is :—

1. Inco-ordination of the two elements of the

autonomic system producing localized spasm of both muscle layers of the bowel.

2. Secondary changes in the mucosa, at first catarrhal, later more severe inflammation.

3. Absorption of protein through a disordered mucosa which would not pass through healthy membrane.

4. This foreign protein circulating in the blood increases the excitability of the vagus.

5. Disturbance of the autonomic balance and completion of the vicious circle.

This view is supported by the fact that aperients which hasten bowel movements excite attacks of asthma, etc., in the susceptible, and that clinical relief may be obtained by cleansing the bowel with non-irritants such as compounds of kalene and liquid paraffin or lactic acid and bile-salts. Relief may also be obtained by administration of pepsin and hydrochloric acid to increase the digestion of protein.

This change in the bowel mucosa is the basis of Oriel's observation that abnormal amino-acids circulate in the blood of asthmatics and that a proteose is secreted with the urine. But it is quite illogical to assume that the amino-acids are the primary cause of the asthma, and to attempt to desensitize the patient with the proteose. The prime cause is the increased sensitivity of the autonomic nerves, and there is a more reasonable approach to this point along anatomical lines both normal and morbid.

This point may be made clear by a recitation of

some of the results of experimental excitation of the vagus described by physiologists. These are :—

a. Contraction of bronchi and increase of bronchial secretion.

b. Augmentation of intestinal movements and increase of glandular secretion.

c. Alteration of blood-sugar level. McLeod and Clark show a fall in this level comparable with that found in asthmatics by H. C. Cameron. If this is due to stimulation of the pancreas and liberation of insulin, it has a bearing on the presence of eosinophilia, Lawrence having shown that injection of insulin causes eosinophilia.

d. The last paragraph has an obvious bearing on acidosis and alkalosis.

e. Acetylcholine is liberated at the vagal nerve-endings.

Vagal overaction in allergics cannot be excluded as a factor in producing the alterations in K and Ca ratios, and the indefinite and conflicting results of workers in this field may be due to the fact that they are dealing with a variable cause—namely, varying degrees of autonomic imbalance.

Researches are being carried on into the relationships of the above findings—blood-sugar level, eosinophilia, *p*H level, etc.—to the allergic states, with the object of discovering the basic cause. But if the asthma, eosinophilia, and the rest are the results of the same stimulus, no amount of correlation will discover the cause of any. Furthermore, the perfection of experimental technique acquired in these

researches is of little value to the clinician, whereas the correlation of minute physical signs, of personal and family history, with the allergic states is not only likely to provide a truer conception of the basic causes, but would be an infinitely more valuable training to the able young research scholar who will eventually have to earn a living in the practice of clinical medicine. The search should therefore be made for that which makes the autonomic nerves, the so-called 'bronchial centre' of Hurst, more than normally sensitive, and the simple anatomical approach seems hitherto to have been much neglected.

The Psychological Element.—Psychologists regard the 'toxic idiopathies' as 'anxiety neuroses.' They can quote experimental evidence, such as the attack of asthma on seeing an artificial rose in the patient whose original attack was caused by that flower, and the dog which vomited at the sight of a hypodermic syringe after an emetic had once been injected with that instrument. Their statements, however, are sometimes capable of another interpretation, such as that in the *Report of Progress, Asthma Research Council*, 1934, p. 7: "In some cases children were over protected as a result of being much wanted children, e.g., the first girl after a series of miscarriages."

While not disputing the existence of asthma due solely to anxiety neurosis, I submit that if the vagus or the 'bronchial centre' of Hurst is rendered irritable by organic disease in itself or its immediate neighbours, the psychological stimulants are more likely to cause

the so-called allergic states. Be it remembered here that the sympathetic elements now so often excised by surgeons are commonly found to be diseased—i.e., the seats of low-grade inflammations.

Endocrine Disorder.—Sir Humphrey Rolleston has said that it was tempting to invoke endocrine origin for the allergic states, particularly the thyroid or adrenal, and that strong evidence has been adduced to show that failure of adrenal secretion is the cause.

With the deepest respect it is suggested that adrenal deficiency is coincident and not a cause, and that Warthin's statement that the adrenal in the female is as frequently the seat of syphilitic infiltration as is the testicle in the male deserves more attention than it has received.

In Chapters II and III I have attempted to show the significance of syphilis in disorders of the thyroid, and it is the object of this and the two following chapters to show the relation of the same disease to the allergic states. It is not so much a matter of opinion as of anatomy and demonstrated pathology.

METHODS OF TREATMENT OF THE ALLERGIC STATE

Having mentioned some of the conditions commonly associated with allergy, let us pause for a moment to recall an oft-used analogy and to classify the methods of treatment.

The analogy may be expressed in the words of Sir James Dundas-Grant: "Hypersensitiveness (the allergic state) is an explosion, but it requires a

detonator." He finds the commonest detonator in the nasal cavity. It is agreed that the explosive is the autonomic nervous system. The elements which activate the detonator are foreign proteins, pollen, etc.

A disproportionate amount of attention is being paid to the activators and detonators and too little to the explosive. This is shown by the current methods of treatment, which are of three kinds :—

1. Methods concerned with the activators. The body is desensitized by increasing doses of the appropriate protein, or non-specifically by injections of liver extract. On the same principle the body can be educated to tolerate snake venom and arsenic.

2. Methods concerned with the detonator. Cautery of nasal mucous membrane, alimentary hygiene, etc.

3. Methods neutralizing the explosion, such as adrenalin.

But what methods are directed to the most important element, the explosive—the autonomic nerves? X rays are used empirically, but this method is not universally available and not free from risk. I submit that it is successful because it corrects a paravertebral chronic adenitis which is the actual irritant of the nerves. The universal use of iodides in asthma is also empirical, and probably acts on the adenitis primarily. Similarly hydrotherapy, as practised on the Continent, by clearing up the associated bronchitis, is followed by a subsidence of a focal adenitis.

Recently Carranza and other workers in Lowenstein's laboratory in Vienna have sought to associate asthma

with tuberculosis—the bacillus being found in the blood of 13 out of 21 asthmatics. One must remember that Lowenstein himself has declared that he has isolated Koch's bacillus from the blood of approximately 70 per cent of people taken at random, and that he and his colleagues have ascribed a tuberculous origin to many diverse clinical states.

There is no real conflict between this view and the writer's. The difference is geographical. The essential factor is that the autonomic system is rendered sensitive by a neighbouring adenitis. The infecting agent in some is tubercle, in others syphilis, in a still larger group the pyogenic and other organisms in chronic bronchitis.

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CHAPTER V

ASTHMA

THE cause, or associated disease, in 44 cases of asthma is tabulated below.

	No. of Cases
Idiopathic, cause undiscovered	9
True allergic, all due to hay	3
Associated with chronic bronchitis, etc.	9
Associated with nasal disease :—	
Chronic catarrh 1	
Polypi 5	7
Vasomotor rhinitis 1	
Doubtful syphilis	9
Syphilis	7
Total	44

Of the above idiopathic group, three developed chronic indigestion of the regurgitation-flatulent type after cessation of the asthma.

No useful purpose would be served by a recital of the clinical features of the first four of the above categories, except to say that all the allergics were apparently cured by avoidance of hay and desensitization with pollaccine, and that three of the cases associated with chronic bronchitis were apparently cured by autogenous vaccines.

The outlines of the two syphilitic groups are given below.

ASTHMA AND SYPHILIS

Case 1.—Female, 52, farmer's wife. Asthma for twenty years. Eleven children, no miscarriage. Unequal reacting pupils. Heart enlarged to right, and irregular chronic fibrosis of lungs. W.R. weakly positive. Relieved by iodides. Sudden cardiac death two years later.

Case 2.—Female, 59, housewife. Was asthmatic for several years in middle life. Now complains of headache. Pupils miotic and sluggish. Right pupil is oval. Weakness right side of face. Knee-jerks +. Five brothers and sisters died in first year of life, three survived to adult life.

Father died of diabetes. Mother died of cancer of the uterus. C.S.F. faintly opalescent and deposited a flocculus. Diagnosed congenital syphilis with recovery.

Case 3.—Female, 32, housewife. Bronchial asthma for four months attributed to being knocked down by a motor-car. When seen for an insurance company she had an adenoma of the thyroid, tremor, pulse 96. The outline of one pupil was irregular. Her only child, six weeks old, was marasmic, snuffly, and desquamating. W.R. found strongly positive, and complete clinical recovery followed specific treatment.

Case 4.—Female, 70, housewife. Asthmatic for twelve years from 28 to 40, following pneumonia. 1929: Chronic headache. Tongue milky, smooth, and fibrotic. Signs of myocardial degeneration. Dyspnœa. Pulse 120, irregular. Recovered under specific treatment. 1932: Epigastric mass with symptoms resembling carcinoma of stomach. Recovered under mercury and iodides. Heavy longitudinal ribbing of finger- and toe-nails. Small hard adenoma of thyroid with retraction of right upper lid. W.R. negative, but husband is positive.

Case 5.—Male, 80, master mariner. Chronic bronchitis and asthma. W.R. +.

Case 6.—Female, 78, wife of above. Also chronic asthmatic. Their only daughter has chronic bronchial catarrh. She had five successive miscarriages before specific treatment was given and followed by a living apparently healthy child.

W.R. negative in mother and daughter.

Case 7.—Male, 56, mariner. Was asthmatic for thirty years, then retired and went to South Africa. Spontaneous recovery from asthma, but developed acid dyspepsia—retching and loss of

appetite every morning. Does not take alcohol. Has intermittent claudication of the legs and a perforated nasal septum. Claudication and dyspepsia relieved by mercury and iodides.

Mother has perforated nasal septum, primary optic atrophy, smooth milky fibrotic tongue, and atrophic scirrhus of breast. She recovered from crippling multiple arthritis with potassium iodide.

ASTHMA AND DOUBTFUL SYPHILIS

Case 1.—Female, 21, shop assistant. Has been under observation for twelve years, and was originally regarded as a subacute infective endocarditis. This diagnosis was supported by clinical signs and a history of acute rheumatism. She remained a semi-invalid for eight years. Then, when she was 18, all her permanent teeth became carious within a short period, the entire enamel being shed. The diagnosis was now changed to congenital syphilis with recovery, and she is now in permanent employment. At the age of 20 she dragged her left foot for three weeks and had difficulty with speech as if her tongue was too big for her mouth. Both hands and feet were cyanosed and congested. No plantar response on either side. Large puckered scar in left epitrochlear region attributed to septic vaccination in infancy. True spasmodic asthma developed in twentieth year. She was a foundling, and adopted by a woman who had anæmia and splenic enlargement, apparently cured by a long course of arsenic by the mouth.

Case 2.—Female, 54, housewife. Asthma and cardiac arrhythmia came on at menopause. Nervous, thin, high-coloured type, subject to vomiting of dark bile. Pupils are unequal, but react. Tongue is pale and smooth with rectangular fissures, but not fibrotic. She has had five miscarriages and no living children.

Husband has had hyperpiesia and precordial pain for several years.

Case 3.—Male, 49, commercial. Was asthmatic from 8th to 21st years. Aortic regurgitation. Symptoms relieved for one year by mercury and iodides, then died of cardiac failure after attack of ' cardiac ' asthma.

Wife: No children or miscarriage. Unequal reacting pupils. Recurring lumbar fibrositis, tinnitus, palpitation, flatulent dyspepsia have been satisfactorily treated with mercury and iodides.

Brother: anæmic, hyperthyroid. Unequal reacting pupils. Two attacks of bullous eruption in palms and ulnar borders of hands. Has always reacted well to mercury and iodides.

Case 4.—Male, 52, quarryman. Asthma and bronchitis since youth. Sought treatment for pain in right knee, thigh, and fingers, and generalized multiform rash. Personal examination negative for syphilis. Treated with mercury and iodides, and has had no further asthma for five years.

Both parents, one brother, one sister said to have died of phthisis. Sole surviving sister had bilateral cataract, a smooth milky tongue with dorsal scar, W.R. +, and a retroperitoneal tumour from which she eventually died.

Case 5.—Female, 18, at home. Asthma and chronic catarrhal deafness. W.R. negative. General facial type suggests congenital syphilis. Clinical recovery on mercury and iodides.

Case 6.—Female, 45, housewife. From 1924 to 1928 was treated for neurasthenia and flatulent dyspepsis. In 1928 began to have chronic bronchial catarrh. In 1930 became asthmatic—diagnosis of intrathoracic neoplasm on X-ray evidence. Discrete glands in both posterior triangles of neck. Nasal polypi with empyema of both antra and ethmoiditis. Required ten to twelve injections of adrenalin daily. In 1934 had complete nasal operation without decided relief of asthma. Thoracic shadow disappeared under mercury and iodides and bismuth injections. Asthma better; still requires one injection, sometimes two, of adrenalin at night.

Mother has miotic pupils with irregular outlines. Unilateral exophthalmos with ptosis recovered under mercury and iodides. W.R. +.

Case 7.—Male, 18, schoolboy. Farmer's son. Asthmatic for years. Several brothers and sisters lost in infancy, and one miscarriage. Patient has spleen enlarged to three fingers below costal margin. W.R. negative. Sensitive to seven foreign proteins out of thirteen tested. During ten weeks' treatment with iodides and arsenic had one attack only.

Case 8.—Female, 36, housemaid. For two years has had swelling of legs and pain in calves on walking—claudication type. Flatulent dyspepsia and obstinate constipation for years. Has 'mucous colitis'; sometimes passes nothing but mucus, occasionally a little blood. Occasional attacks of choking dysphagia. Adenoma of isthmus of thyroid. During treatment had right-sided facial neuralgia and puffiness of eyelids. Complains of angry blotchy patches on neck and arms when she washes. Urine normal.

Both parents died of cancer, otherwise personal and family history negative.

Very great improvement after treatment with mercury, iodides, and bismuth injections. Patient can walk freely, and now (two months after cessation of treatment) complains only of occasional nocturnal asthma.

Case 9.—Female, 22, housewife (*Case* 4 in the angioneurotic œdema group described later). She was the youngest of three survivors of fourteen children ; the others died in infancy.

Father was a master mariner, and both he and his wife were asthmatic for as long as the patient can remember.

CONCLUSION

Syphilis is a strong potential cause of asthma for the following reasons :—

1. General adenitis terminates the secondary stage. For reasons given in the INTRODUCTION this adenitis is most marked in the thorax.

2. Syphilitic lymphadenitis has been shown by cardiologists to be the cause of aortitis, and at the same time has been shown to possess some degree of activity throughout the so-called latent period.

3. It is not possible that the aorta is the *only* one of the anatomical relations to be affected by the adenitis.

4. The autonomic nerves, particularly the vagus and the bronchial centre of Hurst, are immediate anatomical relations of the lymph-chain, and are affected in the same way as the aorta.

5. Clinical evidence, and the therapeutic test, support the hypothesis that syphilis produces asthma in many of its victims.

6. This has remained unrecognized because of the widespread neglect of latent and late congenital syphilis.

CHAPTER VI

VASOMOTOR DISTURBANCES

VASOMOTOR disturbances, as described in this chapter, may be tabulated as follows:

Exudative	Angioneurotic œdema
	Purpura
Spasmodic	Blanching of extremities
	Congestion of extremities
	Claudication

THE EXUDATIVE GROUP

The authors of the article on angioneurotic œdema in Osler & McCrae's *Modern Medicine* have no doubt that in both this condition and in purpura the lesion is essentially the same, with a qualitative difference: in the one case serum is exuded, in the other red cells. The writer of the article on purpura, however, hardly refers to this point, but rather emphasizes the biochemical tests necessary to differentiate the several types of purpura. This would be more valuable if it led to effective treatment, but the patient seems to be no better off when it is known that he suffers from thrombocytopenia. It is notable that in these articles no mention is made of syphilis, though other authors have shown that this disease plays an important part in chronic urticaria. Neither angioneurotic œdema, chronic urticaria, nor purpura

is more than a symptom, and it should be so regarded by the family physician. Osler himself taught that these conditions were essentially the same disease, and the present writer submits that the common controlling factor lies in the sympathetic system in a large proportion of cases. It is not necessary to exclude entirely Bloch's theory of a circulating toxin acting locally, for some cases are certainly explicable on this basis.

Assuming then that a disorder of the sympathetic nerves is often responsible, there are two strong reasons for excluding chronic syphilis in all cases. In the first place Hazen and other American writers have shown the frequency of a positive Wassermann reaction in chronic urticaria and the response to specific treatment. Secondly, the pathology of syphilis accounts satisfactorily for each feature of the syndrome. The process may be visualized thus :—

1. Syphilis latent in paravertebral lymph-glands.

2. Slight ebb and flow of chronic inflammation (the so-called lymphocytic infiltrations) irritate the neighbouring chains and ganglia.

3. Hyperæmia or mechanical pressure disturbs the nerve elements, and vasomotor effects are displayed peripherally.

Whatever the exact mechanics may be, there is a parallel in the somatic nerves when referred pain, trismus, spasmodic torticollis, etc., result from irritation of nerves by lymphadenitis.

Although the cases here described form too small a series from which to generalize, it includes all the

FIG. 4.—Finger-nails of case of angioneurotic œdema. W.R. ±. Cured by specific treatment.

cases which have occurred in my practice during the thirteen years under review. The associated signs and the response to treatment indicate the place of syphilis. That this disease is not more often recognized in its chronic stage is due to the dependence placed on the Wassermann test; the large majority of adult congenital syphilitics and at least three-fifths of the latent tertiary cases, in whom the Wassermann reaction is negative, thus escape proper diagnosis.

A period which produced 196 cases of thyroid dysfunction, showed only 13 of angioneurotic œdema and 6 of purpura.

ANGIONEUROTIC ŒDEMA

Case 1.—Female, 54, housewife. Run-down and anæmic. Epigastric pain and vomiting; habitually takes McLean's powder. Crops of erythema nodosum, subcuticular dusky-red painful swellings. Intermittent angioneurotic œdema of face and neck severe enough to prevent her looking after her small shop. Finger-nails dystrophic (*Fig.* 4). W.R., 2 M.H.D. (weakly positive). Childless wife of a sailor. Relieved by specific treatment.

Case 2.—Female, 4. Angioneurotic œdema 2 years. Mother is typical congenital syphilitic.

Case 3.—Male, 28, motor-driver. During three months his face had become swollen and puffy on three occasions. During the previous twelve months he had attacks of itching of the hands, legs, and body. After scratching, urticarial wheals appeared. Variable enlargement of thyroid with mild hyperthyroidism. Epitrochlear glands palpable. W.R. negative. Cured by bismuth injections.

Case 4.—Female, 22, housewife. For fifteen months had attacks of massive urticaria on chest and arms which had resisted treatment elsewhere. Father a master mariner. Patient the youngest of three survivors of fourteen children. All others died in infancy. Both parents asthmatic. Patient has a symptomless adenoma of thyroid. W.R. negative. Cured by bismuth injections and mercuric iodide pills.

Case 5.—Female, 38, housewife. Giant urticaria of face, arms, and torso. Has not been well for three or four years—myalgic pains, headache, sleepless, giddy. Pupils miotic but react. Subthyroid type. Refused injections and was treated on orthodox lines. Relieved after six months. W.R. negative.

FAMILY HISTORY.—Father died of ascending paralysis—bedridden for three years. Mother died of a series of strokes. One brother died of phthisis, another is inmate of an asylum. One sister died of " St. Vitus's dance in heart and hand ". One sister died at 26 of phthisis with enlarged heart; X rays showed transverse diameter of heart increased by one half, and prominent aortic shadow. Four sisters died in infancy. Of two surviving sisters one has been cured of chronic abdominal pain by specific treatment after several years of invalidism.

Case 6.—Female, housewife. Seen when visiting a general hospital. She had been admitted for tracheotomy for acute œdema of the larynx, and was known to be the subject of recurrent angioneurotic œdema. She was anæmic and a subthyroid type. At the writer's request a Wassermann test was performed and found positive. The ophthalmic surgeon found confirmatory evidence in the fundus oculi.

Case 7.—Female, 46, farmer's wife. Anæmic, thin, chronic abdominal pain. Tender aorta. Angioneurotic œdema widely distributed and present for many years.

Husband died at 54 of cerebral degeneration after fits which began at 48. No tumour. No alcohol.

Two years after course of bismuth, reports that no further swellings have occurred, and that abdominal pain has ceased.

Case 8.—Female, 13, schoolgirl. Transitory swellings in face and legs. One attack in tongue. Said to have had albuminuria; none present on examination. Vesicular eruption of left shin. Glands in neck, axillæ, and groins said to have been present for seven years. Attended once only.

Case 9.—Male, 52, grocer. Eleven months urticaria. Came on after eating lobster. One attack attributed to aspirin, others to beef and strong tea. Relieved for a time by peptone injections. No signs suggestive of syphilis and not relieved by bismuth.

Case 10.—Female, 42, housewife. Always complaining. Rheumatic pains, creaking knees. No children. No signs of lues. Transient œdema of eyelids and lips. Had no further attack of

swelling during the year which has followed a course of bismuth injections and mercuric iodide pills.

Case 11.—Female, 59, housewife. Urticaria recurrent. Has had swelling of tongue on three occasions. No signs of lues. No specific treatment.

Case 12.—Male, 40, railway clerk. Urticaria three years. Tremor, flatulent dyspepsia, idiosyncrasy to aspirin. Not luetic.

Case 13.—Female, 14, schoolgirl. Formerly had had infantile eczema. No signs of lues.

Comment.—Of the 13 cases, Nos. 1 to 6 showed evidence of syphilis, but only in Nos. 1 and 6 was this acquired. In the remainder it was congenital. The five cases treated on specific lines were quickly relieved; the remaining one (No. 5) treated on lines suggested by a consultant was relieved more gradually; indeed it is admissible to suggest that in this case the disorder followed the natural tendency to cure which is characteristic of many of the symptoms of latent syphilis.

Case 3 had been diagnosed elsewhere as nephritis and certified unfit for work. Albuminuria is known to occur occasionally with angioneurotic œdema, and possibly led to error in this instance. When examined by the writer there was no albuminuria or other sign of nephritis. Blood-pressure and renal function tests were normal. He had, however, a combination of other signs indicating latent congenital syphilis—plicate tongue, epitrochlear glands, unequal reacting pupils, and slight hyperthyroidism.

The response to specific treatment was immediate and lasting.

In *Case* 5 the diagnosis rests on the family history.

Case 6 illustrates the prevailing attitude of the profession to this subject. The surgeon was content to relieve the respiratory distress, and the family doctor, though aware that his patient was syphilitic, had not connected the œdema with that disease.

There are minor suggestive features in one or two of the remaining cases, but the series taken as a whole illustrates the necessity of excluding syphilis in cases of angioneurotic œdema.

Purpura

The purpuric rash tends to spontaneous cure, thus conforming to the behaviour of many other features of latent syphilis which depend on the ebb and flow of the typical infiltrations. In addition to the vaso-motor disorder permitting exudation, it is necessary to assume a disorder of the spleen altering bleeding and clotting times and the number of thrombocytes. The writer has not met a severe hæmorrhagic case in his own practice, but of the 6 cases of milder type, 4 were syphilitic, and the other 2 not above suspicion. The common senile type is not included.

Case 1.—Male, 70, sailor. History of chancre without later symptoms. Knee-jerks absent. Pupils miotic and irregular in outline. W.R. +. Two attacks of purpura, generalized distribution, patches up to 1·5 cm. diam. Duration four weeks, ambulant.

Case 2.—Male, 35, schoolmaster. History of syphilis with full course of treatment. W.R. negative. Severe generalized attack of purpura, with dermatitis of shins. Required hospital treatment. Has remained well three years.

Case 3.—Male, 46, clerk. One severe attack of purpura. History of infection twenty-one years ago. W.R. +. Early tabes and delusional insanity. Arrested by specific treatment.

Case 4.—Female, 64, housewife. Notes available over a period of twenty-eight years' chronic ill health. Positive W.R. not discovered till an overhaul eight years ago.

1906: Weakness all over, palpitation, enlarged liver. Tender all over abdomen. Gave a history of vomiting for twenty years. Hepatic enlargement treated empirically with mercury inunctions.

1914: Epigastric pain; anæmia; emaciation; tumour in left hypochondrium—(?) stomach, (?) spleen.

1915: Epigastric pain and vomiting.

1918: Dyspnœa, epigastric pain, profuse night-sweats. B.P. 170.

1921: Albuminuria with swelling of hands and feet.

1929–34: General improvement. Always has discomfort in splenic region.

1933: Three attacks of purpura—small, widely distributed patches. Ambulant.

Case 5.—Female, 55, wife of sailor. Childless. No signs. One attack seven years ago. Confined to bed.

Case 6.—Female, 65. Three years' history of anorexia, vomiting, and anæmia. Tongue smooth, pale, fibrotic. Palpable mass found in epigastrium. *Blood-picture:* pernicious type—a macrocytic anæmia; colour index 1. W.R. negative. Recurrent, large, widely-distributed purpuric patches. In three months had apparently recovered on specific treatment. Returned three months later with recurrence of symptoms and mass in epigastrium, and died, presumably of carcinoma of stomach, nine months after first attendance.

In addition to this series, the writer has twice observed petechial hæmorrhages of the bowel at laparotomy. One case was an acute syphilitic appendicitis, and the other a gastrectomy for jejunal ulcer following gastro-enterostomy. In the second case the W.R. was negative, but the syphilis became manifest in the central nervous system seven years later.

THE ANGIOSPASTIC GROUP

This group comprises blanching, congestion, and claudication.

A single cause of sympathetic irritation may produce not only blanching or congestion of the extremities, but apparently unrelated states such as asthma, spastic colon, effort angina, and the vascular changes already described.

It is a criticism often levelled at the syphilologist that he attributes all kinds of symptoms to the spirochæte, but here the object is to establish this organism as *a*, not *the*, common recognizable irritant of the sympathetic chain, and the criticism should rather be directed to writers on the above-named states, and especially on allergy, who so completely and persistently ignore the potentialities of the lymphatic stage of syphilis.

The mechanics of blanching are self-evident—the spasm of vessels is sufficient to cut off the blood-supply. Those of congestion are similar, but the spasm is less in degree; the blood-supply is not completely cut off, but is so slowed that the *vis a tergo* is lost and blood stagnates in the smaller veins. This point is illustrated in *Case* 1 below, where a band of pallor crossed the adjoining halves of the proximal and middle phalanges. Distal to this band the fingers were dusky red, while proximal to the band was a normal flesh colour. Minor degrees of blanched fingers such as follow immersion in cold water are regarded as physiological, and no case severe enough to deserve the name of Raynaud's disease has been met with.

In this section a simple record of cases will achieve the object of this chapter, for it shows syphilis in 7 cases out of a total of 26, and probable syphilis with response to specific treatment in 6 others. *Case* 1 is placed first on the list because, although probably not syphilitic, he exhibited the greatest variety of symptoms of autonomic dysfunction which it has been the writer's lot to meet. All the symptoms were relieved by removing the single cause.

BLANCHING GROUP

Case 1.—Male, 43. Long-continued anxiety and emotional stress. By nature highly sensitive, alternately high-spirited and despondent. Blanching of fingers and dermatographia. 'Colitis' resisted treatment for several years until treated as secondary to spastic colon. Recurrent bronchitis. Finally invalided by effort angina and claudication in the feet. This patient showed no signs of syphilis and recovered under symptomatic treatment and removal of the cause of anxiety neurosis.

The family history, however, while not suggestive enough to afford a diagnosis of third-generation syphilis, has elements which would prevent the adoption of an alternative etiology. His father was prematurely old, and fell dead off a bicycle at 54. His paternal uncle died of cerebral degeneration. His paternal aunt had fifteen miscarriages and no living children. Her husband was syphilitic: W.R. + and post-mortem evidence. The aunt herself showed no signs of syphilis, but apparent cardiac failure and the coma of cerebral sclerosis were overcome by small doses of iodides.

Syphilitic.—

Case 2.—Male, 45, quarryman. Feet always cold and white, cannot get them warm even before a fire. Sweats profusely at night. Persistent precordial pain without physical sign. W.R. + +, and child has typical congenital facies.

Case 3.—Female, 56, housewife. A tertiary syphilitic. W.R. +. Two months after commencement of treatment both hands went white. At the same time she had precordial pain. After three months' treatment said she had not felt so well for years. During

the following three months had several attacks of blanching of fingers, each of which lasted two or three hours.

Doubtful Syphilis.—

Case 4.—Female, 47, housewife. Neuralgia of face confined to left infra-orbital region and to a spot 3 in. above left ear. Continuous pain above the umbilicus, a tight feeling. Night sweats troublesome. Intermittent blanching of all the fingers; may come on when she is sitting down, and is independent of room temperature. Symptoms had persisted for several years, and patient had been to a teaching centre for consultation. She was childless, and the daughter of a master mariner who died at 50 years of age of sudden heart failure. On these slender grounds she was treated as a congenital syphilitic, with success.

Case 5.—Female, 58, housewife. Pain in left shoulder and arm. Occasional faints. Fingers became numb and white. Subthyroid type. Seven years later presented masses of enlarged glands in both supraclavicular fossæ. Refused biopsy. Apparently cured by 914. W.R. negative. Died one year later of subarachnoid hæmorrhage.

Non-syphilitic.—

Case 6.—Male, 54, journalist. Fingers white and numb in the morning. Head flushed and hot. Feet cyanosed in distal halves. Occasional numb feeling in the legs. B.P. 180/100. Palpable arteries. No signs of syphilis. Relieved by Lugol's iodine.

Case 7.—Female, 42, housewife. Aphonia. Invalided by muscular debility. Hands become blanched on slightest provocation, e.g., brushing hair, reaching for telephone. Legs too heavy to lift. Ankles blanched. Believed to be hysterical. Is a cancerphobe, and both parents died of cancer. No response to any form of treatment.

Case 8.—Female, 68, widow. Fingers blanch from time to time without apparent cause. Pain and tenderness in epigastrium, cannot bear weight of bedclothes. X rays: gastro-intestinal tract normal. B.P. 200/90, musical systolic bruit. Relieved by iodides. Pain returned one year later after violent bout of coughing.

Case 9.—Female, 49, housewife. Blanching of fingers and distal half of feet on exertion, e.g., act of rising from or going to bed. Multiple signs of toxæmia; central scotoma with temporary loss of right half of visual field. Albuminuria; rheumatic pains

in joints. Neuritis of shoulder-girdle with wasting of muscles. Sense of severe burning behind the sternum. Pads of great toes feel raw. Iodides produce nodules resembling erythema nodosum. Treatment: Appendicectomy, irrigation of empyema of antrum of Highmore. Long course of bismuth injections and Hutchinson's pills plus symptomatic remedies. Ninety-five per cent recovery has lasted three years.

COMMENT.—This case is regarded as a type of Bloch's circulating toxin. The appendix was symptomless, but enlarged, white, and rigid, and, judged by the subsequent clinical course, was the toxic focus.

Case 10.—Male, 69, farmer. Dyspnœa. Recent Raynaud type of attacks in all four extremities. Right foot will remain blanched all night; fingers only when he washes—recover after exercise. Onset co-incident with mediastinal neoplasm, from which he died.

COMMENT.—It is reasonable to say that the vasomotor changes here were secondary to irritation of the sympathetic chain by malignant infiltration.

Case 11.—Male, 55, quarryman. Middle and terminal phalanges of fingers white and insensitive, arteries thick and tortuous. Relieved by small doses of iodine.

Mother has same kind of fingers.

CONGESTIVE GROUP

Syphilitic.—

Case 1.—Male, 45, quarryman. Unable to work because of ataxia. Multiple signs of syphilis, including W.R. + in both serum and C.S.F. Coldness and venous congestion of the left foot came on during treatment. Recovered and has now been at work for seven years.

Case 2.—Male, 25, quarryman. For one year had epi- and hypogastric pain, headache, and deafness. Personality said to be changing. W.R. found positive in C.S.F. during hospital routine and was followed by specific treatment. Both feet were cyanosed, congested, and cold even in bed. Recovered and has now been at work eight years.

Case 3.—Male, 68, foreman. For a year or more feet "burn" when he walks and compel him to rest. They are blue and congested. Pes cavus a recent development. Epitrochlear glands enlarged. Tongue fibrotic and milky. W.R. +. Moderate relief only.

Doubtful Syphilis.—

Case 4.—Male, labourer. For four years unable to work because of pains in legs and feet. These are blue and congested. Bilateral pes cavus. Tongue smooth and milky. W.R. negative in serum and C.S.F.

Wife died of carcinoma of œsophagus after seven years' dysphagia: one child, two miscarriages. Became fit for work after three months' specific treatment and remained so for three years.

Case 5.—Male, 55, quarryman.

1928: B.P. 230/110. Pain in chest. Hard cough. W.R. negative.

1929: Swelling in palm of right hand. Right foot œdematous and congested. Pains sharp and shooting up both legs.

February, 1931: Paralysis of intrinsic muscles of right hand, wasting of muscles of right shoulder-girdle. Right pes cavus.

December, 1931: Attack of cardiac asthma. Thought he was dying, strong aortic diastolic bruit developed.

1932: Died of heart failure following aortic insufficiency.

Case 6.—Female, 38, housewife. Scleroderma in tendo Achillis region. Both feet blue and congested. Subject to chilblains. Used to have fits as a child. Ulcerating flat papilloma of base of tongue, treated at radium centre as carcinoma. Unequal reacting pupils. Says two years later that she is quite well.

Case 7.—Male, 39, clerk. Hands and feet always cold and red. Early pes cavus. Fibrotic tongue. Unequal reacting pupils. Heavily ribbed finger-nails. Right plantar reflex is extensor. Cardiac arrhythmia in attacks lasting up to one hour.

Father died of locomotor ataxia. Mother anæmic, smooth tongue, has had dysphagia for solids for more than twenty years.

Non-syphilitic.—

Case 8.—Male, 66, quarryman. Left great toe is blanched, remainder of both feet congested. Pupils unequal; react to light and accommodation. Abdominal, cremasteric, and plantar reflexes absent. Peroneal sensation subnormal on left side. Relieved for several years by iodides. Finally died of congestive heart failure.

Case 9.—Female, 49, housewife. Blueness and coldness of legs with muscular weakness were the first signs of endothelioma compressing lower thoracic cord. When warmed the legs became uncomfortably hot. Coldness of the feet at night was the last symptom to disappear after operation.

Case 10.—Female, 54, housewife. Weakness. Afraid of everything. Sleepless. Will wake suddenly with a sensation of something rising from epigastrium to head, and then appears to be semi-conscious. Sense of pulsation in the epigastrium. Cries all day. Toes and fingers cyanosed in early morning.

Mother was asthmatic and died in melancholia. Only child is hyperthyroid.

Very slow course, but patient attributes her recovery to the specific treatment.

Case 11.—Female, 46, farmer's wife. Hands said to go blue-black. At time of note right little finger was deeply cyanosed but warm to touch. Hyperthyroid. Has had chronic appendicitis several years and refuses operation.

Claudication Group

Syphilitic.—

Case 1.—Female, 50. Persistent pain in feet on walking. Has tried arch supports and strapping without relief. Was treated for syphilis twelve years ago. Choroiditis, and W.R. +. The foot pain was completely relieved by a short course of mercury and iodides.

Case 2.—Male, 56, retired mariner. Perforated nasal septum. Mother has multiple signs of lues. Anæmia and indigestion in patient were relieved by mercury and iodides—the claudication was relieved in a longer time.

Non-syphilitic.—

Case 3.—Male, 60, clerk. No sign of lues. Some calcification of arteries. Relieved by long course of iodides.

Case 4.—Male, 44, quarryman. Disabled by claudication. Mitral stenosis with arrhythmia. History of rheumatic fever. Recovered, and has had no return for six years. Not syphilitic.

REFERENCE

Hazen, *Jour. Amer. Med. Assoc.*, 1916, lxvii, 1650. Out of 100 cases of chronic urticaria, 33 had a positive Wassermann reaction and were cured by specific treatment.

CHAPTER VII

NOTES ON NERVOUS DYSPHAGIA, WITH SPECIAL REFERENCE TO ITS CAUSE

SINCE Vinson published his work on hysterical dysphagia in 1921, much has been written on the nervous disorders of the œsophagus. A review of some of this work in the light of experience gained in general practice leaves a strong impression that the disease has been regarded too much as a local condition, whereas it is a local manifestation of a general disease. I am prompted to write on the subject by L. J. Witts' article on achlorhydria and anæmia in the *Practitioner* of March, 1930, which contains an important statement open, I believe, to question.

The local pathology of achalasia has been established by Hurst. It is a lymphocytic infiltration of Auerbach's plexus in the œsophageal wall, which terminates in fibrosis and destruction of the nerve-cells. The end-result is closure of the lower end of the viscus, with dilatation of the thoracic part, a state which may be produced experimentally in cats by section of the vagal branches to the organ (Cannon). In practice, as may be expected, disorders of swallowing due to cellular infiltrations which embarrass, but do not block, reflex arcs, are much more common than the

final stage of achalasia. With these symptoms are found others caused by similar cell infiltrations and fibrosis in other parts of the body.

From a perusal of the work of Hurst and others on this subject, it would appear that they describe the same condition from different angles and use various terms. Munro Cameron, in his account of dysphagia with anæmia, says there is a variability in the position and degree of spasm, and that Plummer calls it ' hysterical dysphagia', while Brown Kelly and Paterson use the term ' spasmodic contraction of the pharyngo-œsophageal junction '.

It is instructive to trace the growth of our knowledge of the pathology underlying this syndrome. In 1921 Vinson, in a study of 69 cases, concluded that it was hysterical and due to errors of diet. Irwin Moore, in an exhaustive paper on the pathology of dilatation of the œsophagus, suggested no cause, and in the long discussion which followed, the disease was treated as a purely local condition.

By 1926 the pathology was becoming more defined. G. W. Rake described a case of compensated achalasia and demonstrated microscopically that all the local tissues showed early and late changes associated with subacute or chronic inflammation, this being most evident in the ganglia of Auerbach's plexus. The accent again is on the local condition, but Rake's patient was admitted for carcinoma of the tongue, and from the post-mortem findings he was evidently also suffering from a general disease, probably latent tertiary syphilis. In 1927 Brown Kelly reviewed the

subject from the point of view of the laryngologist. All the symptoms and signs which he gives are local, and, he adds, " as far as my own knowledge of this disease extends, there is nothing in the majority of patients that calls for medical treatment." He agrees that the responsible morbid change is a fibrous degeneration of the muscular coats and gangliated plexuses.

In the same year (1927) Hurst wrote on achalasia, but some statements in these articles showed that the last word on the subject remained to be spoken. He says there that the underlying pathological changes may be due to tabes, peripheral neuritis, or reflex irritation. Later, he says : " Presumably it is impossible to restore relaxation to the closed cardiac sphincter." This may be true for the final degenerative stage ; it cannot be true for the pre-degenerative or irritative stage. Indeed, as will be seen, medical treatment in the early stages is satisfactory. He also mentions a patient " who was fortunate enough to have his condition diagnosed correctly on the actual day of onset of symptoms—passage of a bougie on a single occasion produced a complete and permanent cure." This must have been either a temporary spasm or an early case where the causative cellular infiltration ended in resolution instead of fibrosis. It has the merit of indicating the lines on which medical treatment should proceed.

In 1929 Munro Cameron wrote his account of dysphagia with anæmia, and, as already indicated, expressed the opinion that it is allied to the hysterical dysphagias and spasmodic contractions of

other authors. In this paper the general aspects of the disease gain recognition. Secondary anæmia, Hunterian glossitis, and enlargement of liver and spleen are mentioned. Discussing etiology, he asks whether the dysphagia is the cause or the effect of the anæmia, and says that Mayo Clinic workers also have difficulty in being sure. His view is that age and sex are the principal factors. Debility and anæmia, associated with the climacteric, lead to changes in the mucosa, which in turn cause dysphagia. Then limitation of food aggravates the anæmia and leads to enlargement of the spleen.

Later, in March, 1930, L. J. Witts attributed the anæmia found in this condition to achlorhydria. That cannot be correct, because free HCl was present in every one of Munro Cameron's twenty-five patients. It seems clear that the conditions known as ' hysterical dysphagia ' (Vinson and Plummer), ' spasmodic contraction of the œsophago-pharyngeal junction ' (Brown Kelly and D. R. Paterson), ' dysphagia with anæmia ' (Munro Cameron), and ' achalasia ' (Hurst) are closely related and have a common origin—if, indeed, the terms do not refer to the same disease affecting different parts of the œsophagus.

The underlying lymphocytic infiltrations are not limited to the œsophagus, but are to be found in the heart, aorta, liver, suprarenal glands, and elsewhere, as seen in sections in *Appendix B*.

These infiltrations are indistinguishable microscopically from those which Warthin states are pathognomonic of chronic endosyphilis, and there is clinical

evidence in support of the hypothesis that these changes are low-grade syphilitic lesions, possibly in the second or third generation of inherited lues.

It may be said that there are two working methods of clinical research :—

1. In one a syndrome—say, anæmia, glossitis, and dysphagia—is studied, its associated signs are noted, and the cause is sought. Pursuing this method, Suzman came to the conclusion that this syndrome is a deficiency which is dependent on a gastric abnormality. Experience, not logic, discovered a successful remedy in iron.

2. In the second method of research a pathogenic agent is taken—for example, the *Treponema pallidum*—and the disabilities which affect its victims are noted. These disabilities will not necessarily be due to the spirochæte, but if in the course of years all cases of anæmia, glossitis, and dysphagia are found to be related to the organism in the way to be shown here, it becomes necessary to ask if these symptoms are not direct remote results of syphilis.

It is all the more necessary because the factors required to produce the syndrome are present in the established pathology of latent syphilis. Up to now, most if not all of the application of the pathology of lues to clinical medicine has been done by cardiologists and neurologists.* Internists have not sufficiently

* 1. COOMBS, C. F. (*Quart. Jour. Med.*, 1932, Jan., 183).—"The periaortic origin of [syphilitic] aortitis is recognized. The cellular infiltrations which are its distinctive mark well out of the mediastinal lymphatics in the direction of the aorta, and are piled up on the outer surface of the adventitia."

realized that destructive infiltrations which proceed from the lymphatic system of the thorax and attack the aorta and spinal cord must inevitably affect also the œsophagus and its nerves. It may be said in passing that the same process in the abdomen invades the sympathetic ganglia, but the consequences are not described in medical text-books, nor applied to the problems of nervous dyspepsia, spastic colon, etc.

The anæmia of the syndrome is referable to the

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2. KLOTZ, O. (*Amer. Jour. Med. Sci.*, 1918, clv, 92, 98).—" It is from the two main lymphatic drainage beds, the thoracic and the abdominal, that the syphilitic virus comes to be distributed to particular segments of the aorta. It was unusual to find lymph-glands enlarged to such a degree that they would attract attention clinically and pathologically. Not difficult to demonstrate chronic mediastinitis, which had a distinct course along lymph-channels to and from the glands. By thus localizing in the mediastinum, the syphilitic virus has an opportunity of attacking to a greater or less degree the important visceral contents of this division of the thorax, of which the most important and accessible is the aorta."

3. MARTLAND, H. S. (*Amer. Heart Jour.*, 1930, Oct., 10).—" The lungs, on account of their great capillary area, have received a greater dosage [of spirochætes] than any other organ except the skin, and must clear themselves in a different way. Many organisms pass through into the systemic circulation, many are slowed up in the lungs. Many pass by lymphatics into the peribronchial and mediastinal glands. The latter become reservoirs for storage of spirochætes. The mediastinal theory is supported by X-rays showing the fuzzy border of periaortitis and the melting away of this with specific drugs. The heart signs in the earlier stages of syphilis (tachycardia, bradycardia, and arrhythmia) are due to involvement of the cardiac vagus and sympathetic nerves, and to psychic causes, more than to actual myocarditis."

Blood changes in syphilis relevant to the anæmia-dysphagia syndrome :—

4. *System of Bacteriology*, viii, 211 (Med. Research Council).—" Diminished number of red cells. Pronounced reduction in hæmoglobin. More severe forms including pernicious type (Andrewes). Considerable variety of blood changes, simple anæmia with and without splenic enlargement. Polycythæmia and pernicious type, both with enlarged spleen." (Eason.)

well-known changes in the liver, spleen, and bone-marrow. It would simplify the study of the anæmias if an attempt were made to define the types due to syphilis, having special regard to the modifications of the disease which result from latency, immunity, attenuation, transmission in latent stages, and heredity.

As already mentioned, the early writers on dysphagia and anæmia focused attention on the œsophagus, and almost ignored the general condition of their patients. Agreement was gradually reached that the dysphagia is due to cellular infiltrations destroying Auerbach's plexus, and the general condition of the sufferers received more notice. Witts (1931) gives a list of associated symptoms: "General constitutional weakness most evident in the digestive, reproductive and nervous systems, frequent winter coughs and pleurisy, rheumatoid arthritis, headache, pruritus, nervous breakdown, insanity. Sterility, complete or relative, miscarriages and post-partum hæmorrhages, enlarged spleens, spoon-shaped nails, chronic paronychia, erythema induratum. In many cases the disease is a hereditary abnormality."

This is a concatenation of symptoms familiar to the student of chronic latent syphilis, but it is unfortunate that under the existing organization of the profession only the family doctor has the opportunity to observe this stage of the disease. Between the end of the secondary stage and the onset of recognizable aortitis or tabes, the clinical picture is slowly unfolding itself, but can only be perceived by patient note-taking over periods of years.

Hurst and Rake discuss the etiology and say: "The factor or factors concerned in its production are unknown . . . syphilis as an etiological factor was discussed in the first case described by Rake, and one of Hurst's early cases had signs of tabes, but the blood gave a negative Wassermann reaction." Thus the diagnosis of syphilis is rejected because the Wassermann reaction is negative and for no other reason, although it is known that a negative reaction is found in three out of five latent syphilitics.

A safer avenue of approach to this problem would be to discover the effect on the œsophagus, the thoracic sympathetic chain, and the vagus nerves, of that infiltration from the lymphatic glands which exists in all chronic syphilitics, and which causes destructive lesions in the aorta of 80 per cent of male cases. Is it not possible that the relative immunity of the female to aortitis is accompanied by a greater vulnerability of the sympathetic? Is it possible that the œsophagus and its nerves can escape a process so destructive to its immediate neighbour?

Before giving details of cases I should like to say that I approach this subject as an observer of chronic familial syphilis, and to record the *experience* that the syndrome of anæmia, glossitis, and dysphagia occurs in daughters, granddaughters, and wives of syphilitics. It is not strictly confined to the female sex, nor would I claim that syphilis is the only cause—but this is the only disease with a pathology known to be capable of producing the symptoms, and specific treatment in the early stages is highly satisfactory.

Case 1.—Male, aged 60. Progressive dysphagia, marked clinical anæmia, gastric analysis not done. W.R. + +. Fibrotic smooth tongue. Aortic regurgitation.

COMMENT.—A syphilitic. Dysphagia became complete and he was regarded as a carcinoma of œsophagus. Post mortem: wall of œsophagus smooth throughout. Pathological report: "Thyroid gland and wall of œsophagus are the seat of a squamous-celled carcinoma. It is not possible to define the seat of origin. The growth was not obstructing the œsophagus, and its presence was not suspected until microscopic sections were cut."

The dysphagia was probably paralytic owing to involvement of the vagus nerve. If, instead of paralysis of the œsophagus, he had had bilateral abductor paralysis, an assumption that this was due to syphilis of the same nerve would be both reasonable and acceptable. A malignant growth too small to be recognized macroscopically could not account for the grave clinical anæmia, and therefore this case is anæmia, glossitis, and dysphagia, due to some cause other than malignant disease and reasonably attributable to syphilis.

Case 2.—Female, aged 49. Seven years' history of food sticking in upper part of gullet with pain and choking. Moderate anæmia. Spleen enlarged. Tongue had large atrophic patch on either side. Sore angles of mouth. Pupils unequal. Knee-jerks feeble with reinforcement. Abdominal reflex and ankle-jerks absent. Plantars both extensor. Cerebrospinal fluid, W.R., 1 M.H.D., otherwise normal. Serum W.R. negative. Husband is syphilitic. Two miscarriages. Father and maternal female cousin died of carcinoma of œsophagus. Female cousin has nervous dysphagia. Post mortem: sections of aorta show lymphocytic infiltration spreading between the laminæ.

Case 3.—Female, aged 50. Recurrent feelings of obstruction in gullet behind manubrium sterni. 1,120,000 red cells, picture resembling pernicious more than secondary anæmia. No free HCl. Tongue smooth and pink, *deep fibrosis* is shown by inability to protrude, and by appearance of furrows when effort is made. Crops of ulcers in the mouth with attacks of dysphagia. Sore angles of mouth. *Pupils unequal. Aortic regurgitation.* Serum W.R. negative. Cerebrospinal fluid 0·2/1000 protein, 6 lymphocytes per c.mm. *W.R.*, 2 *M.H.D.* Therapeutic result good, but always relapsed when it was stopped.

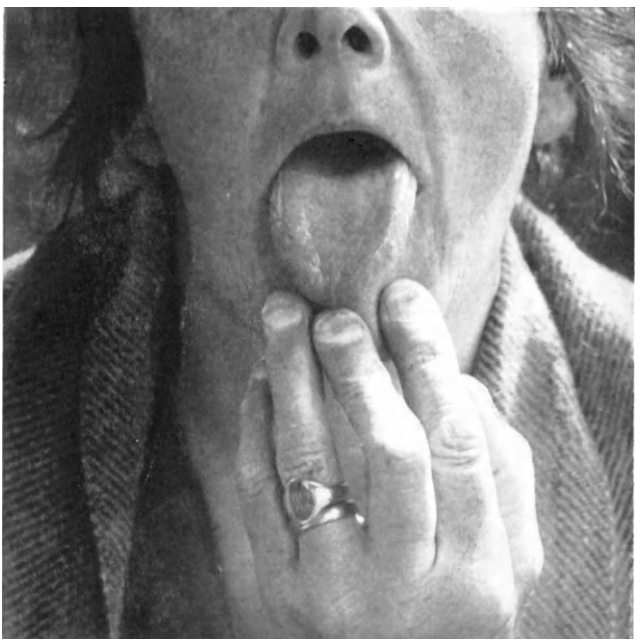

FIG. 5.—*Case* 5. Showing condition of tongue and finger-nails.

FIG. 6.—*Case* 6. Showing condition of tongue and thumb-nail.

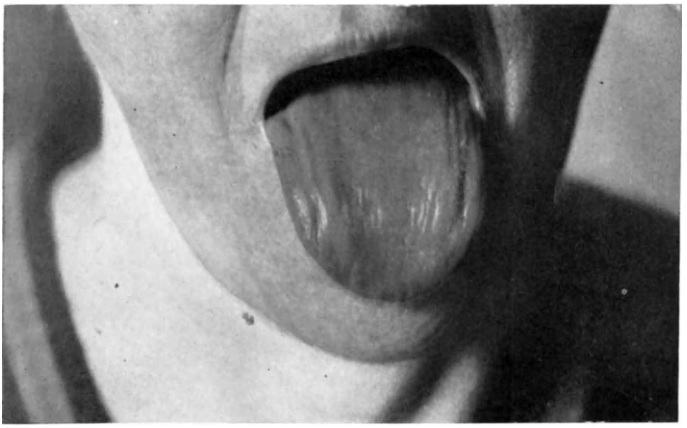

FIG. 7.—*Case* 8. Showing condition of tongue.

FIG. 8.—*Case* 8. Showing spoon-shaped nails.

COMMENT.—A syphilitic. Dysphagia became complete and he for a diagnosis of syphilis.

Case 4.—Male, aged 29. Cannot swallow because of burning pain behind sternum. No free HCl. 2,760,000 red cells, resembles pernicious more than secondary anæmia. Tongue red, raw, and sore in marked contrast to general pallor. Sore angles mouth. Four laparotomies for chronic abdominal pain. Sister has forward bending of shafts of tibiæ. Another sister has notched incisors. W.R., 1 M.H.D.

Case 5 (*Fig.* 5).—Female, aged 44. Has not been able to swallow meat, pills, or similar solids for many years. Living on slops. No free HCl. 2,350,000 red cells. Hb 24 per cent. Cerebrospinal fluid 0·45/1000 protein, 9 lymphocytes per c.mm. Otherwise normal. Tongue has mother-of-pearl plaque on either side ; painless ulcer margin ; spoon-shaped nails ; chronic punched-out ulcer of leg. Therapeutic response good.

Case 6 (*Fig.* 6).—Female, aged 60. No dysphagia. 2,420,000 red cells. Hb less than 25 per cent. No free HCl. Tongue smooth, fibrotic, with rectangular fissures. Spoon-shaped nails. W.R. negative at first, became weakly + after three months' treatment and clinical recovery.

Case 7.—Female, aged 50. Great difficulty with food on account of burning in gullet. Occasional inability to swallow. Hb less than 40 per cent. No free HCl. Had partial gastrectomy in 1929. Argyll-Robertson pupils. Tongue atrophic and fibrotic, with mother-of-pearl plaques. Sore angle of mouth. Has spastic colon. Therapeutic response good.

Case 8.—Female, aged 44. Dysphagia—sometimes can swallow nothing at all. Tiredness. Night sweats. Tongue typical (*Fig.* 7). Spoon-shaped finger nails (*Fig.* 8). Reds 1,950,000. Hb 30 per cent. Picture of secondary anæmia. Anæmia for six years, dysphagia for two years. Has been taking iron and cannot get on without it. Husband an early tabetic, primary infection twenty-two years ago. First child lost at five weeks, second at six months ; three others look well, eldest eleven years. Clinical cure in three months.

Case 9.—Widow, aged 41. Sudden onset eighteen months ago when she could swallow nothing for three days. Relieved by bougie. Since then cannot swallow meat or potatoes, these stick behind the sternum and are regurgitated in 10 to 15 minutes with

much mucus. Glossitis, anæmia, tachycardia, and extrasystoles. W.R., 1 M.H.D. Has remained symptom-free for six years after bougie dilatation and mercury and iodides.

Case 10.—Widow, aged 61. For many years has had trouble with swallowing, worse lately. She has spasms in which she cannot swallow even saliva. Smooth tongue, anæmia, anæsthesia of ulnar nerve-trunks. W.R. negative. Apparently cured by mercury and iodides.

Case 11.—Female, married, aged 58. As long as she can remember she has had to leave crusts, and cut meat fine. Eight years ago had an acute attack of dysphagia and has since lived on slops. Smooth tongue, severe anæmia, persistent moist fissures at angles of mouth. Persistent tachycardia, 120–140. Palpable spleen. W.R., 1 M.H.D. No children or pregnancy.

Husband had precordial pain which was relieved by a course of mercury and iodides. Treatment unavailing because of development of carcinoma of œsophagus. Post-mortem examination showed patchy perihepatitis and enlarged spleen. Liver shows atrophy, mainly portal in distribution, fibrosis, and lymphocytic infiltration. Suprarenal gland shows atrophy and lymphocytic infiltration. Aorta shows fibrous change and lymphocytic infiltration about vasa vasorum.

Case 12.—Female, aged 55. Complete loss of appetite for twelve months. Food appears to stick opposite angle of Louis. Typical smooth tongue, chronic moist fissures at angles of mouth, pronounced anæmia, unequal pupils. Tachycardia and arrhythmia. W.R. negative. Relieved for seven years by mercury and iodides.

Case 13.—Female, aged 61. Sudden onset of dysphagia in 1927. Complete, unable even to swallow water. Second attack a week later. Third attack after twelve months. In 1930 attacks became frequent and severe, lasting for several days at a time. Normal tongue, fissures at angles of mouth. Anæmic. Pupils unequal but react. Knee-jerks absent. W.R. negative. Five miscarriages. Treatment consisted of bougie dilatation on two occasions, with a course of bismuth injections and mercury and iodides. Bismuth repeated at her own request. Has remained well for five years.

Of the foregoing cases of anæmia with dysphagia, all except the last one had glossitis in addition.

In spite of the favourable effects of mercury and iodides it is not at first apparent that they were the victims of low-grade syphilis—but it is certain that the disease was general and not local. When, however, they are compared with undoubted syphilitics showing similar signs, the luetic diagnosis has very carefully to be considered and emphasis laid on family history. Recent examples of these symptoms in syphilitics are the following :—

Case 14.—Male, aged 30. Complete dysphagia came on one week after fractured base of skull. W.R. found positive in C.S.F. and serum. Gradual and complete recovery following intravenous arsenic.

Case 15.—Female, aged 21. Intermittent attacks of dysphagia for five months with pain behind sternum. Low pyrexia throughout, tachycardia, tremors, unequal reacting pupils. W.R. +. Relieved by specific treatment.

Case 16.—Female, aged 23. Sharp pain in epigastrium. ' Swallow ' feels sore. Food sticks like a stone behind lower part of sternum and then goes down. Also has trigeminal neuralgia, chronic low pyrexia, tachycardia, and unequal reacting pupils. W.R. +. Believed to be congenital, as father's W.R. is +.

Case 17.—Male, aged 55. A tabetic with all the features except dysphagia, namely : glossitis, anæmia, moist fissures at angles of mouth.

The high incidence of malignant change recorded in these pages corresponds to the accounts of other observers. It is not out of place to mention the hitherto unexplained correlation between syphilis and cancer of the œsophagus noted both in the Registrar-General's tables and in the Medical Research Council's report on occupational cancers. In Holmes's words : " One quite unexpected correlation came to light

between syphilis and cancer of the œsophagus . . . later figures have lent still more support to the idea of a connection between the two." If both the dysphagia-anæmia syndrome and syphilis are thus related to cancer of the œsophagus, they may be related to one another. Possibly this inter-relation is seen in truer perspective in family practice where the several generations and collaterals are under observations for many years. In any case the family history thus gained is essentially more valuable than that given by a patient or gleaned from follow-up questionnaires.

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CHAPTER VIII

SYPHILIS AND NERVOUS DYSPEPSIA

THE etiology of dyspepsia, whether due to organic disease or functional disorder, is not yet established on a satisfactory basis. Reference to two authoritative lectures will serve to give the modern British opinion on this problem. Bolton[1] (1928) gave as the causes of the pyloric syndrome :—

1. Indigestibility of food.

2. Hyperacidity of gastric juice with predisposing causes in the nervous system, these being : (*a*) Direct effect upon mesenteric plexuses by chronic ulcer, etc. ; (*b*) Reflex irritation from elsewhere in the alimentary tract ; (*c*) General conditions such as neurasthenia.

In a leading article the *Lancet* referred to this lecture in these terms : " That we are still very far from understanding this large group of clinical symptoms is evident if only from the frequency with which they resist all forms of treatment." Bolton's lecture embraced both organic and functional disease.

Hutchinson[2] (1931), in a paper read before the Royal Socity of Medicine, dealt only with the nervous dyspepsias, classifying them into three groups :—

1. Those of psychoneurotic or central origin due to mental disturbance or anxiety states.

2. Those due to fatigue apart from mental perturbation.

3. The group in which no disorder of function in the stomach could be demonstrated, where possibly surgical exploration had proved negative, but where patients constantly complained of symptoms referred to the stomach.

Neither in Bolton's paper nor in the discussion which followed Hutchinson's opening was any reference made to latent syphilis. In this respect there is a marked contrast between British and American opinion. Kilduffe[3] writes: "The latent syphilitic is as likely as not to seek medical advice for symptoms not at all suggestive of syphilis on their face value, for stomach trouble, vague and ambulatory pains, high blood-pressure, etc., and all too often he receives treatment for just that of which he complains." Stokes and Brown[4] gave details of 200 syphilitics whose main complaint was stomach trouble, with the classical tale of heartburn, belching, pain, nausea, and indigestion. Thirty-five of these underwent needless operation. More significant from the point of view of this paper is their statement, that during the period of their investigation 50 per cent of the patients admitted to the Mayo Clinic with a diagnosis of neurosis of stomach or functional stomach proved to be latent syphilitics.

In this country L. W. Harrison[5] argues that syphilis of the stomach is becoming more prominent, and says

that an essential step in the investigation of any patient presenting prominent gastric symptoms is to examine him for syphilis.

How can we account for this striking difference of opinion? L. W. Harrison, in a personal communication, says he knows of no current research on the clinical side of latent syphilis in this country. Syphilologists know the possibilities, but the patients have passed out of their hands, and generally do not reach those of the neurologists until destructive lesions of the nervous system are far advanced. This interregnum is of much importance to the patient, and it is during this prolonged period that he is likely to suffer disturbances of digestion.

Nervous dyspepsia may be classified into two main groups :—

1. That due to disordered function brought on by fatigue, anxiety, psychic trauma, etc.

2. That due to organic disease of the controlling nerve elements. The great example is the gastric crisis of tabes, but there is established pathological basis for a much more numerous class—that class described by the aforementioned American workers. At the end of the secondary stage the spirochæte is swept up from the blood-stream and confined to the lymphatic glands, where, for the rest of the patient's life, host and virus maintain a state of unstable equilibrium. When conditions favour the virus it leaves the glands, and its egress is marked by cellular infiltrations along the lymph-channels. Cardiologists have demonstrated these infiltrations, and have shown

how their action over a period of years produces destructive aortitis. Not only the aorta but all neighbouring structures are attacked, and of these the sympathetic chain is both the most important and the most vulnerable. Kiss has shown that these nerves occasionally traverse the substance of glands in addition to being in close proximity throughout their course. Any chronic inflammation of the lymphatic glands may irritate the sympathetic, and thereby fulfil Bolton's second group of postulates. It has been said that a high index of suspicion helps the diagnosis of syphilis. In the present instance suspicion is grounded on pathology and justified by the therapeutic test.

When analysing the notes of 100 consecutive cases of latent syphilis I found that 21 referred their symptoms to the abdomen, and it therefore appeared that not only is latent syphilis a cause of so-called nervous dyspepsia, but that digestive disturbances are the commonest symptoms of which latent syphilitics complain. It is, however, difficult to draw a clinical picture of these cases; duodenal ulcer, gastritis, or gall-stones may be closely imitated. The common feature is that they do not respond to treatment for these conditions. Evidence of syphilis is usually found in other members of the family. For instance, one woman resisted treatment for years until her husband developed general paralysis of the insane. Her Wassermann was negative, but she promptly responded to bismuth injections. A man showing no signs of syphilis was not relieved of vomiting and

epigastric pain until specific treatment was given because his wife had ten miscarriages and no living children. In a third case the mother had anginal pains and a perforated nasal septum, while the daughter had flatulent indigestion and acidity with fern-leaf tongue.

In the 21 cases the Wassermann was positive only 3 times, and weakly positive in 3 others, but one single sign of somatic or neurosyphilis is enough to justify treatment. Thus two cases had fixed inequality of pupils; one had had symptomless hæmaturia five years previously; another had absent knee-jerks associated with unequally reacting pupils and a smooth patch on the tongue.

Treatment is successful unless inflammatory irritation of nerve ganglia has been succeeded by fibrosis and destruction. Early recognition based on a knowledge of the pathology of latent syphilis is therefore of great importance, and the main lesson is that there is no feature to distinguish syphilitic dyspepsia, but when dyspepsia occurs in a latent syphilitic it is essential to treat the syphilis.

The pathological changes described by Warthin are capable of causing dyspepsia in two ways:—

1. Direct stimulation of the sympathetic nerves such as causes the inequality of reacting pupils often found in these patients.

2. Interference with the normal reflexes by infiltrations in the sympathetic ganglia. Those which Hurst describes about Auerbach's plexus in achalasia of the cardia seem to me to be indistinguishable

microscopically from those which Warthin describes as pathognomonic of latent syphilis. The general conclusion is, therefore, that a tangible proportion of the nervous dyspepsias are caused by latent syphilis, and that it is advisable to exclude this disease before resorting to psychotherapy, such as was advocated in the discussion following the Hutchinson paper.

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CHAPTER IX

SYPHILIS AND THE 'CHRONIC ABDOMEN'

AND ITS BEARING ON THE OPERATION OF ABDOMINAL SYMPATHECTOMY

THE term 'chronic abdomen' is applied to conditions causing persistent symptoms, without organic lesions in the lumen of the bowel or in other viscera. In practice this is a large class very resistant to treatment, though recently sympathectomy has been applied to some cases with success. This operation is available only for cardiospasm, pylorospasm, and colospasm, and is not always successful even in these sub-groups. It has been established that the excised nerve-chains are diseased, but no evidence is forthcoming as to the nature of the disease. Lawrence Abel says that emotion is the prime etiological factor—the sequence being sympathetic overaction, hyperæmia, cellular infiltration, fibrosis, permanent damage to ganglion cells. Before surgeons attribute scars to emotion other possible factors should be excluded. One of these factors is latent syphilis. This disease is known to produce two groups of pathological changes capable of causing the chronic abdomen—namely: (1) Plastic peritonitis, localized or generalized; (2) Chronic paravertebral adenitis inevitably affecting the sympathetic chain by propinquity. These pathological

changes form the basis of this chapter, and are thus described by authorities.

McDonagh speaks of thickening of the peritoneum in chronic syphilis with involvement of subjacent tissues, and formation of adhesions. In some cases there is perihepatitis with pain independent of food and with frequent vomiting.

Warthin says: "Throughout the prevertebral tissues, root of mesentery, along the radicles of the portal vein and in the pelvic tissues there constantly occur in the bodies of old syphilitics minute perivascular infiltrations of lymphocytes and plasma cells, associated with fibroblastic and angioblastic proliferations and fibrosis of a more or less marked degree."

In Chapter VII (p. 84) reference is made to Martland, Klotz, and Carey Coombs, who have shown how, at the end of the secondary stage, spirochætes are swept into the paravertebral lymph-glands, there to remain in a state of unstable subjection for the rest of the patient's life.

The diagram copied from Kiss (*Fig.* 9) shows how intimately this chain of glands is related to the sympathetic ganglia and how the virus of latent syphilis located in the glands can affect the ganglia. It is clearly necessary to exclude a prevalent disease before attributing localized proliferations of lymphocytes and subsequent fibrosis to emotion (Abel). The routine procedure in hospital practice is to perform a Wassermann test and to dismiss the diagnosis of syphilis when the result is negative, without regard to the oft-established fact that three-fifths of latent

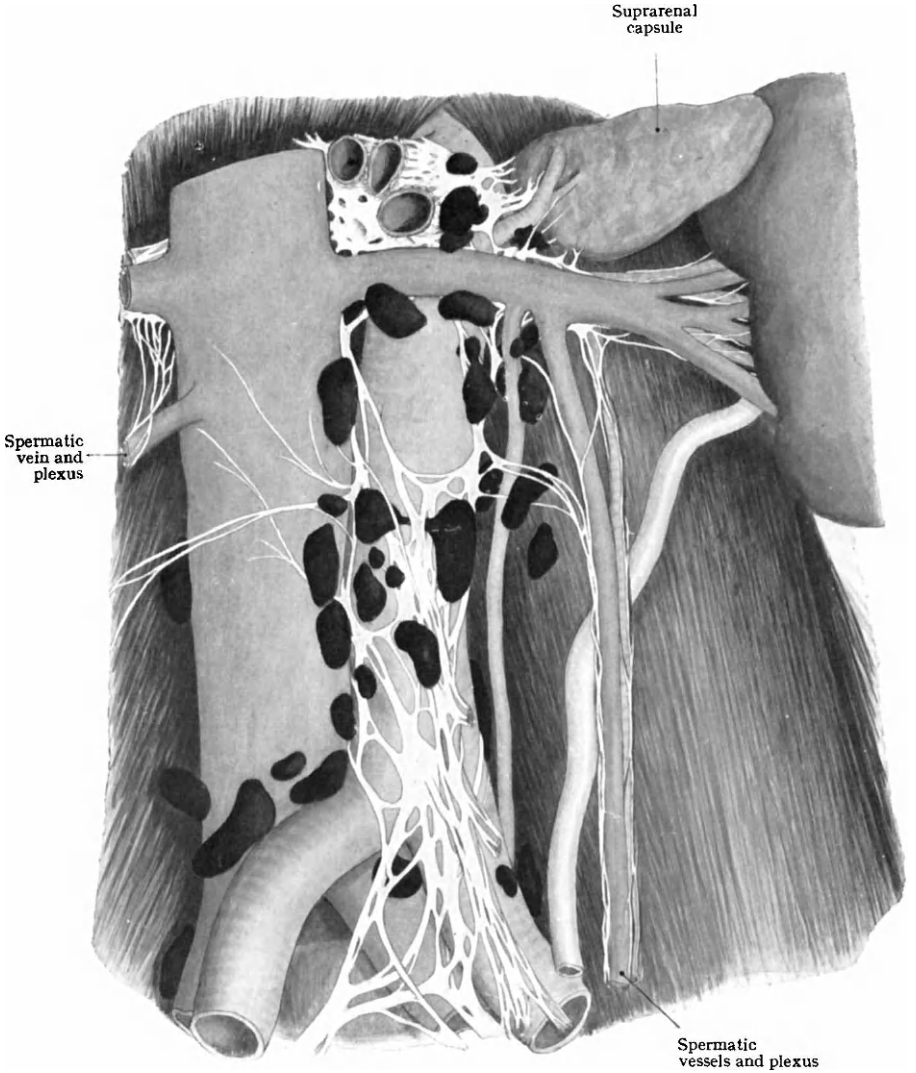

FIG. 9.—Mesenteric lymph-glands and the sympathetic. Showing the relationship between the lymph-glands in the region of the abdominal aorta and the lumbo-aortic plexus of the sympathetic. (*After Kiss.*)

and tertiary syphilitics have a negative reaction, and ignoring the fact that a negative reaction is the rule in adult congenital syphilitics.

The diagnosis of syphilis is more often missed because a Wassermann reaction is negative than made because the reaction is positive, and for that reason alone the test should cease to occupy its present position of decisive authority. I am not concerned with gastric ulcer due to gumma, but with syphilitic infiltration of lymph-glands producing gastric symptoms by interfering with sympathetic nerves.

Admittedly this etiology is highly controversial, and I will therefore first describe cases which have been investigated by teaching hospitals without diagnosis or benefit, but which have subsequently been relieved by injections of bismuth and administrations of mercury and iodides.

Case 1.—Female, aged 43, unmarried.

HISTORY (Nov. 9, 1932).—For two years she has had pain referred to the umbilicus and through to the interscapular region, variable in time and in relation to food; sometimes caused by food, at others a glass of milk will relieve it. Wakes her up at night. Nausea, giddiness, constipation. Sore tongue for months. Has been kept on milk diet for twelve months without relief.

Past Medical History.—Operation for hæmorrhoids, 1920. Appendicectomy at a Teaching Hospital, 1930. Re-admitted for persistent symptoms, 1931. Tonsils removed after negative X-ray examination of gastro-intestinal tract. Nervous breakdown for six months during 1931.

Family History.—Negative.

ON EXAMINATION.—Well covered, good colour, anxious expression. Tremor, tachycardia, moist skin. Unequally reacting pupils. Tender aorta. Tongue normal in appearance. No other physical sign. W.R., 1 M.H.D.

Improvement began immediately. There was a temporary relapse six weeks later, when she vomited all day after eating fried ham, and the next night had wind all night after taking gruel. The same night she had an acute piercing momentary pain in the right lower lumbar region.

A year later she reports that she has been quite well and at regular work ever since.

COMMENT.—A combination of low-grade hyperthyroidism with unequally reacting pupils and a sore tongue added to an indigestion which had defied treatment from the best hands, led to a diagnosis of chronic endosyphilis and clinical recovery. Castex says that syphilis is the commonest cause of hyperthyroidism among Argentinians. I have reported 100 cases of unequally reacting pupils, of which 50 were in syphilitics or their immediate relatives.

Case 2.—Female, aged 24, shop assistant.

HISTORY (Feb. 7, 1930).—Eight years' history of indigestion, vomiting, wind, and constipation. No appetite for breakfast or tea. Would vomit after various foods—e.g., meat and vegetables, poached egg, oranges. Sometimes has epigastric pain and vomit after a simple meal of bread and milk, but none after cold meat and pickles. For constipation she habitually takes 9 gr. of cascara sagrada every night.

Past Medical History.—In 1922 she was an in-patient at a Teaching Hospital, for chronic indigestion; in 1924 an in-patient at a Teaching Hospital, Medical Side. X-ray report states: "Stomach and duodenum normal, normal passage through bowel. Appendix not seen, area very tender on palpation. ? Appendicitis." Appendicectomy was performed without benefit.

ON EXAMINATION.—Pale, podgy, pimply. No physical sign beyond unequally reacting pupils. W.R. negative.

For ten months she was treated for chronic constipation and spastic colon on ordinary lines with moderate improvement.

Dec. 19, 1930.—Vomits after every meal. Palpitation after effort. Heart now showed soft systolic apical bruit with suggestion of gallop rhythm. Second pulmonary sound reduplicated and sharp. First aortic sound roughened and conducted up carotids.

FAMILY HISTORY.—At this stage particular attention was given to the family history:—

Father died of an ascending paralysis after being bedridden for three years.

Mother died after a series of strokes.

One brother died of phthisis, another is inmate of an asylum.
One sister died of " St. Vitus's dance in heart and hand ".
One sister died of phthisis with enlarged heart. X-ray showed transverse diameter increased by one-half and prominent aortic shadow.
Four sisters died in infancy.
Two years later the patient reports her abdominal symptoms relieved; has worked throughout. She complains occasionally of precordial discomfort with dyspnœa and œdema of ankle.

COMMENT.—Lasting relief was not obtained in this case until the combination of family history and transient aortic disease led to specific treatment.

Case 3.—Male, aged 66, sailor.
HISTORY (Nov. 28, 1931).—For eighteen years has had intermittent pain in the right hypochondrium and liver area. Attacks last three or four weeks, with similar interval. Dull steady pain with feeling of deep burning. Also pain in epigastrium; belches, then has sensation of burning in epigastrium. Almost daily attacks of acidity and vomiting.
Past Medical History.—Typhoid twice. Gonorrhœa in youth. In-patient in a Teaching Hospital, July, 1931. Summary of notes: No physical signs. History of alcoholic dyspepsia. X-ray—(1) gall-bladder normal, (2) barium meal. No organic lesion of gastro-intestinal tract.
ON EXAMINATION.—Well covered, weather-beaten. Pupils small, react, left is oval. Abdominal and cremaster reflexes not obtained, others normal. B.P. 240/120. Crepitations low down in both axillæ. Serum W.R., 1 M.H.D.
I made a diagnosis of perihepatitis and treated with specific remedies.
Fifteen months later the patient's daughter, a trained nurse, reported that he had a moderate cerebral hæmorrhage after months of excellent health.

Case 4.—Female, aged 33, unmarried.
HISTORY (Jan. 20, 1930).—Long history of indigestion which became worse three years ago. Abdominal pain, vomiting, severe constipation. The pain is of three kinds: (1) Sense of soreness in attacks lasting two to six days, relieved by vomit. Localized in left hypochondrium and across abdomen, and down the left leg. Sometimes relieved by magnesia. (2) Pain in left lumbar

region associated with frequency of micturition. (3) Dysmenorrhœa for two to three days before the period, associated with vomiting.

Appetite good, but cannot eat because she vomits after everything except toast and bread and butter. Bowels very constipated. Takes large doses of cascara regularly; constipation makes her pain worse. No cough, but is continually spitting up frothy stuff from the stomach.

Past Medical History.—In 1928 was in-patient in a Teaching Hospital. Summary of notes: X-ray of kidneys and urinary tract shows no calculus. X-ray of gastro-intestinal tract shows gastroptosis with suggestion of appendix pathology. Appendicectomy and right ovariectomy performed through muscle split incision.

From 1930 I treated her symptomatically without benefit, and finally performed exploratory laparotomy. There were many localized bands of adhesions between loops of small bowel and between leaves of mesentery. The left ovary was cystic and embedded in the wall of the uterus with normal Fallopian tube. Lesser omentum divided and sutured (Le Rocq). Adhesions divided.

The patient died suddenly two days later from coronary thrombosis.

PATHOLOGICAL REPORT.—The pathologist's report on sections was as follows:—

Aorta shows definite lymphoid infiltration of vasa vasorum and general hypertrophy of all the tissue elements.

Coronary artery, definite lymphoid infiltration, thrombi in smaller branches. Wall of vessel thickened with here and there a rupture of the lining membrane.

Section through cœliac axis artery and ganglia.—Vessels show changes as above. Ganglia show definite lymphocytic infiltration and the parasympathetic tissue shows chronic inflammatory changes in which lymphoid cells predominate.

COMMENT.—This pathological report corresponds with the description of changes due to syphilis by the pathologists mentioned in the first part of this paper. In the demonstrated absence of lesions in the lumen of the bowel the paravertebral inflammation may be accepted as the basis of the symptoms. She was highly neurotic, but I suggest that this was the result and not the cause of the inflammatory changes.

Case 5.—Female, aged 30, married, no children.

HISTORY.—Many years' indigestion; has been going from doctor to doctor for two years. Twelve months ago she had severe pain across the abdomen, with vomiting. Has vomited every morning ever since. Periodic regurgitation of acid in mouth. Hungry, but is afraid to eat because of vomiting. Constipated; takes cascara regularly. Diagnosis, appendix dyspepsia.

OPERATION.—General adhesions in lower abdomen. Appendix completely buried—removed. There was temporary improvement, but nausea persisted and within six months she was as bad as ever.

Admitted to a Teaching Hospital, with provisional diagnosis of chronic endosyphilis.

Summary of notes: Pupils unequal, react. Serum W.R., 2 M.H.D. X-ray of gastro-intestinal tract shows no evidence of organic lesion. *Colon stasis.* Test-meal shows bile and blood absent throughout. Total acid of above normal. Free HCl absent from resting juice. After a quarter of an hour normal. Resting juice 17 c.c. Lactic acid absent. Urine: catheter specimen normal.

DIAGNOSIS.—" Nothing wrong "; the provisional diagnosis of chronic endosyphilis was not seriously considered.

COMMENT.—This patient remains unrelieved. She illustrates the limits of medical treatment, which cannot be expected to correct established fibrosis. Compare the medical treatment of early and established tabes dorsalis. She is, in my opinion, a suitable case for sympathectomy to correct the colon stasis.

Case 6.—Female, aged 50, unmarried.

HISTORY (1923).—History of indigestion for years, attacks lasting two weeks with intervals up to six weeks. Typical duodenal syndrome, with pyloric stenosis and constipation.

Operation.—Showed chronic duodenal ulcer. Gastro-enterostomy and appendicectomy performed.

1926: Symptoms relieved for only a short period, returned with increased severity.

Operation.—Jejunal ulcer demonstrated. Partial gastrectomy.

1929: Symptoms persisted. Constipation more marked. Malignant obstruction suspected.

Operation.—No adhesions. Enlarged glands in mesentery with white patches on them. Spleen enlarged. Three or four feet of jejunum inflamed, with speckling of peritoneal surface by

subendothelial hæmorrhages. Removed gland showed simple inflammatory change and was ignored.

1930–1 : Symptoms persisted, especially the constipation. Malignant subacute obstruction again diagnosed after X-ray examination. Further operation refused.

1931 : Was sent to the country with a hopeless prognosis and came again under writer's care after an interval of seven years.

On Examination.—Secondary anæmia with glossitis. Hb less than 40 per cent. Moist fissure at angles of mouth, spoon-shaped nails, achlorhydria. Distension of spastic colon visible. Wasted and unable to stand without support. W.R., 1 M.H.D.

Three months' specific treatment sufficed to enable this patient to visit friends and to return to her flat in London. Spastic colon and other symptoms persisted in modified degree. She relapsed, and again went through the cycle of X-ray examination, nursing home, etc.

Christmas, 1932 : Returned under writer's care with recurrence of all the symptoms and in addition signs of myocardial degeneration with arrhythmia. Œdema of ankles and dyspnœa. The bowels had not been opened naturally for six months, and morphia was given regularly for pain.

A further three months' treatment enabled this patient again to visit friends and to return to her flat.

Christmas, 1933 : Delusional insanity and Argyll-Robertson pupil noted. The tongue had become fibrotic.

Comment.—During the years of disability every device of modern medicine and the advice of many distinguished consultants were sought in vain. Twice were the symptoms relieved by specific treatment, and this was the only treatment which proved effective.

A deep interest in the case prompted me to mention my views to those responsible for treatment elsewhere, but with no effect. I have only once seen petechial speckling of the bowel at operation, and that was in a syphilitic. It was assumed that the inflammatory glands were secondary to some focus in the bowel. Primary infection of the paravertebral glands with spread towards the bowel was not thought possible ; this would be the pathology if the basis were congenital syphilis. Where, one may ask, does the virus of this disease dwell if not mainly in the paravertebral lymphatic glands ? The behaviour of the virus in the latent stage of the acquired disease makes this location highly probable.

One of the advantages of family practice is the personal knowledge of family medical history. In the present case the

grandfather was treated for syphilis. An uncle, declared moribund from pernicious anæmia by the highest authorities, recovered under treatment with arsenic. In addition he had retinitis, said to be diabetic. The glycosuria remained from 2 to 4 per cent for years without acetonuria and was unmodified by diet. He recovered from coronary thrombosis and had an epithelioma of the pinna removed. The wife of a cousin has anæmia and spastic colon, with unequal pupils and absent reflexes. She also has been relieved by injections of bismuth more than by any other remedy.

In Chapter VIII, "Syphilis and Nervous Dyspepsia" (p. 96), I mentioned the fact that out of 100 consecutive cases of latent syphilis, 21 referred their symptoms to the digestive system. This figure corresponds to that of Stokes and Brehmer.[1] They compared the symptoms of chronic syphilis in railroad men and farmers. In two groups of railroad workers 28 per cent and 22 per cent respectively complained mainly of gastric symptoms. In farmers the incidence was 25 per cent. There is therefore support for the view that indigestion is the most frequent symptom of a common disease.

This, however, is not the opinion of British physicians. I have referred elsewhere to papers by Bolton and Hutchinson (p. 93). In his recent work, *Chronic Indigestion*, Hunt[2] does not mention syphilis at all, though on page 180 he says, "further work on the factors influencing the response to nervous stimulation is undoubtedly needed." A reviewer described this book as "a useful manual in a department where an opportunity for originality and novelty hardly exists."[3]

Not all authorities are as complacent in their attitude to the problem of indigestion. L. W. Harrison[4]

says, " it is clear that an essential step in the investigation of any case presenting gastric symptoms prominently is to examine him for syphilis."

Again, the leader writer in the *British Medical Journal* (1932, Dec. 17) says, " If a routine W.R. were carried out in all cases of gastric ulcer, especially between the ages of 30 and 45, a good many of these would never come to operation."

Advocates of abdominal sympathectomy admit that the excised elements are the seat of chronic inflammation. Dazzled by the brilliance of occasional successes, they appear content to accept *emotion* as a prime etiological factor, and to treat an inflamed nerve by simple excision. The method should rather be to treat inflammation medically while it is still plastic, and finally to excise nerves when their function is permanently impaired by fibrosis, meanwhile maintaining the respect which surgeons have traditionally paid to the posterior peritoneum. The role of chronic paravertebral lymphadenitis in the etiology of aortic aneurysm and tabes dorsalis has been worked out by cardiologists and neurologists. The same pathology is the basis of much abdominal discomfort and endocrine dysfunction. The treatment of election is to correct the cause as early as possible in the disease.

REFERENCES

[1] STOKES and BREHMER, *Collected Papers of Mayo Clinic*, 1921, xiii.
[2] HUNT, THOMAS, *Chronic Indigestion*, 1933.
[3] *Brit. Med. Jour.*, 1933, April 8.
[4] HARRISON, L. W., *Med. Annual*, 1929, 471.

CHAPTER X

ABDOMINAL ADHESIONS IN LATENT SYPHILIS

THE association of abdominal adhesions with latent lues deserves a chapter to itself. Syphilis of other serous cavities, such as the synovitis of congenital and late secondary disease, attracts attention more because it is visible and palpable than because it is painful. It is unreasonable to assume that the largest serous cavity of the body is immune from effusions well known in the lesser cavities. Such a painless peritoneal effusion might easily escape notice, but resultant adhesions are the basis of a chronic ill-defined indigestion, easy to treat in the early stages but extremely resistant to treatment when the adhesions have become organized. Letulle[1] in 1918 described in histological detail chronic syphilitic peritonitis in cases giving a positive Wassermann reaction.

During the past two years I have found such adhesions at laparotomy three times, and, unless this is a coincidence, syphilis should rank second only to tubercle as a cause of the condition.

Case 1.—A sailor, aged 59, for eight years has had symptoms suggesting duodenal ulcer. W.R. +, but no other signs of syphilis. Laparotomy showed no duodenal ulcer, but the whole

cæcum and appendix were buried in friable dull brick-red adhesions easily broken down without hæmorrhage. The appendix was removed, and specific treatment given. Eighteen months later there had been no return of symptoms.

Case 2.—A woman, aged 54, married, no pregnancy, had a strangulated umbilical hernia. Sac contained matted small bowel, which was returned *en masse* as no peritoneal cavity could be found. Convalescence was uneventful at first, but on the eighth day she died suddenly. Post-mortem examination showed that the entire peritoneal cavity was obliterated by soft friable adhesions. Her heart muscle showed typical syphilitic infiltration. Her mother is bedridden, with multiple signs of tertiary syphilis. There was no history of indigestion, and the relatives could not remember any attack of inflammation of the bowels.

Case 3.—A woman, aged 46, married, no pregnancy, had vague abdominal discomfort and urinary frequency. Examination revealed uterine fibroids, and operation was advised. Hysterectomy was difficult owing to multiple adhesions uniting coils of small intestine to each other and to the abdominal wall. Convalescence appeared normal at first, but inequality of the pupils was noted, and Wassermann test showed 2 M.H.D. of complement fixation. When she was due to leave hospital she developed a fever, which proved to be paratyphoid B and ended fatally. Only a vague history of inflammation of the bowels in childhood could be gleaned from the relatives.

Case 4.—A married woman, aged 65. Her case was instructive because the nature of her illness was not suspected during three years' invalidism by five medical practitioners, including the writer. It is only fair to say that thorough examination was never allowed, and throughout the clinical picture was dominated by a congestion of the bases of both lungs. She was in the habit of calling in a practitioner when rather worse than usual. Her gastric symptoms were epigastric pain, occasional vomiting, and long-standing difficulty with food. Post mortem the organs on both sides of the diaphragm were found matted together by firm adhesions, and microscopically syphilitic infiltration was present in all the organs examined.

It is probably inexpedient to treat latent syphilis if symptoms are absent, but it cannot be other than

an advantage to know that a patient is a latent syphilitic, and to apply both specific and symptomatic treatment whenever symptoms appear. I submit that if every patient in whom abdominal adhesions are accidentally discovered at operation were investigated, a large proportion would furnish confirmatory evidence of syphilis.

REFERENCE

[1] LETULLE, M., *Bull. de l'Acad. de Méd.* 1918, lxxx, 209.

CHAPTER XI

SOME CLINICAL FEATURES IN LATENT SYPHILIS

A BRIEF description of cases will show the variety of material and the difficulties of classification. In all the therapeutic test was positive.

Case 1.—A single woman, aged 35, complained of weakness, irritability, and headaches; duration six months, and increasing. There was marked clinical anæmia, an enlarged heart, with systolic apical bruit. B.P. 160/90. Pulse 120, temperature 99° to 99·4°.

A provisional diagnosis of subacute infective endocarditis was followed by appropriate treatment and rest in bed for six weeks. There was no improvement in the condition and the prognosis appeared grave.

In the meantime the following features were observed: chronic painless onychia (also present in the mother), middle-ear deafness on the right side, hypertrophic tremulous tongue, sore angles of mouth persisting for six weeks, and a burning pain behind the sternum. The father had died of 'softening of the brain'.* The mother was subject to attacks of cardiac arrhythmia and anginal pains; she had an enlarged heart, B.P. 170/110, and an aortic systolic bruit.

Examination of the blood and gastric juice of the daughter showed W.R., 2 M.H.D. (= ±) and achlorhydria. Clinical recovery was practically complete after specific treatment, and the patient has remained at work for four years. A persistent trouble was the burning behind the sternum, but that disappeared after twelve months.

The mother has remained free from anginal attacks after a course of potassium iodide. A crippling attack of multiple arthritis disappeared completely under similar treatment.

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* Certified: (1) General debility; (2) Dementia.

This patient shows several features each of which calls for exclusion of chronic syphilis: hypertrophic tongue, roughened lateral margins of nails with slight dried serous exudate, chronic low pyrexia, achlorhydria and anæmia, and chronic moist fissures at the angles of the mouth.

Case 2.—Male, aged 55, stonemason. Complained of sharp pains shooting up the leg, commencing variously in heel, toe, and dorsum of foot. Also a pain gripping him round the abdomen. Duration three or four years. Unable to work.

On Examination.—Very anæmic, smooth milky tongue. Sore angles of mouth. Pupils unequal, react to light and accommodation. Right knee-jerk absent. Left supinator absent. Abdominal reflexes absent (later left lower quadrant became +). Left ulnar nerve trunk insensitive. Distended bladder with residual urine 20 oz. Heart enlarged, heaving impulse. Pulse 100, B.P. 176/100. Œdema of ankles and heavy cloud of albumin. W.R.—.

Three months' treatment was sufficient to restore this man to working capacity. Twelve months later he had been at continuous work, but then complained of a pain shooting up the leg, felt as if he trod on a sharp stone. This was relieved by a short course of bismuth and potassium iodide. It was then noted that cardiac and urinary symptoms were absent, the complexion healthy, and the tongue pink and uniformly covered with small papillæ.

This is the type of case where a negative Wassermann reaction is a bar to proper treatment. He had been treated elsewhere for rheumatism. The difficulty of classifying such cases as the foregoing is great.

In the following pages will be found lists of leading symptoms and clinical signs from 100 consecutive cases; subsequently some of these signs are described in more detail.

The Leading Symptoms in 100 Consecutive Cases

Abdominal pain*	25
Chronic headache	16
Rheumatism of knees	8
Difficulty in swallowing	7

* In three the duodenal type was closely simulated.

THE LEADING SYMPTOMS IN 100 CONSECUTIVE CASES—*continued*

Pain in the back	7
Weakness of a limb	6
Patchy dermatitis	5
Attacks of vomiting	4
Burning behind sternum	4
Bladder weakness and frequency	4
Ataxia	3
Precordial and left hypochondriac pain	2
Raw throat	2
Dry mouth	2
Sore tongue	2
Recurrent loss of voice	1
Congestion of extremities	1
Pain at nape of neck and stiff leg	1
TOTAL	100

WASSERMANN RESULTS

W.R. + (3 M.H.D. or over)	22
2 M.H.D.	11
1 M.H.D.	31
Negative	27*
Not done	9
TOTAL	100

PHYSICAL SIGNS DISCOVERED ON EXAMINATION

Ocular—	
Unequal reacting pupils	50
Corneal nebulæ	3
Lens striæ	2
Bilateral glaucoma and old iritis (each)	1
Central Nervous System—	
Reflexes absent	13
Reflexes unequal	9
Anæsthesia of ulnar nerve trunk	12
Paræsthesiæ: Sensation of cold	4
Paræsthesiæ: Sensation of heat	1
Extensor plantar response	4
Rombergism	3
Clumsy finger movements	1
Staccato speech	1
Lightning pains	1
'Pinching' pains	1
Hyperthyroidism	7
Malignant Disease	17

* In two of these the cerebrospinal fluid was positive.

PHYSICAL SIGNS DISCOVERED ON EXAMINATION—*continued*

Cardiovascular—	
Tachycardia (apart from hyperthyroidism)	18
Temporary bradycardia	1
Auricular fibrillation	1
Gallop rhythm	2
Extrasystoles	2
Bruits (Apical systolic	9
Bruits (Aortic systolic	2
Bruits (Double aortic	1
Pericarditis	1
Coronary thrombosis	1
Varicose veins	6
Congestion of feet	3
Anæmia (usually secondary)	13
Bronchitis—	
Chronic	3
Asthma	2
Chronic basal congestion	2
Nose and Throat—	
Watery nasal catarrh	2
Red dry mucousy throat (Vincent type)	6
Chronic laryngitis	4
Deafness	11
Tinnitus	6
Tongue—	
Smooth and red	7
Smooth and pale	8
Fissured	7
Smooth patches	2
Hypertrophic	4
Sore	2
Angle of Mouth Sore	8
Chronic Low Pyrexia	8

Of these, the most suggestive common signs of latent syphilis are: (1) Inequality of pupils; (2) Smooth, fissured, or fibrotic tongue; (3) Persistent tachycardia; (4) Chronic low pyrexia.

It is not suggested that these are pathognomonic of lues, but that their presence should lead to the deliberate exclusion of this disease.

There are, however, three rarer signs in the list which possibly deserve a moment's thought. They are: (1) Chronic nasopharyngeal catarrh; (2) Chronic

patchy congestion of lungs; (3) Chronic congestion of one or both feet.

Chronic Nasopharyngeal Catarrh

Case 1.—Complained of spontaneous hæmorrhage into prepatellar bursa. No cardiac complaint, but slow irregular pulse and diastolic rub noted. Five days later pulse 102, slapping sounds, no bruit. B.P. 112/75. One year later, pulse 90, B.P. 130/78, second aortic sound accentuated. Syphilis diagnosed at onset because of unequal pupils and fissured tongue. Husband a sailor who fell dead in the street. One year later volunteered that the treatment had cured her catarrh. Has remained well for three years.

Case 2.—Female, aged 38. Husband was syphilitic. Patient showed no signs except anæmia, small mucous patch on tongue, unequally reacting pupils. Catarrh had resisted treatment for many years. W.R., 2 M.H.D. Clinically cured by stabilarsan and bismuth.

Chronic Localized Congestion at Base of Lung not due to Cardiorenal Disease

Case 1.—Male, aged 60. For many years has had crepitations at the base of the lungs, with pyrexial exacerbations every winter. Vaccines, ionization, etc., ineffectual. Has perforation of nasal septum, husky voice, and continually hawks. Has had three or four epileptiform attacks with loss of consciousness; first attack when 28 years of age. W.R. —. For four years after a course of bismuth injections he has remained free from pyrexial attacks, but still has a few basal crepitations. His brother, who also had a husky voice and chronic habit of clearing the throat, died of 'softening of the brain' at the age of 57.

Case 2.—Male, aged 50. Residual basal congestion after double pneumonia, has persisted for four years. W.R. ±

Case 3.—Female, aged 40. For ten years had had a patch of congestion the size of the palm of the hand in the base of the left lung. Two attacks of pneumonia and several exacerbations of the congestion with pyrexia. Vaccines; ionization apparently ineffectual. Since a course of bismuth injections six years ago, she has had no further symptom, though crepitations persist. W.R. —, and no evidence of lues.

Case 4.—Female, aged 65. Invalided for three years by basal congestion. Post mortem, multiple evidence of syphilis which was unsuspected during life.

In this group the subjective effect of bismuth injections is good, although objective signs of congestion have persisted in all cases. I believe that this chronic basal congestion is related to the dense peridiaphragmatic adhesions which are sometimes found post mortem in old syphilitics. However that may be, bismuth injections have benefited all cases of this type in the writer's practice when other forms of treatment have failed.

Chronic Congestion of One or Both Feet

The feet are blue, congested, and cold to touch even in bed. This feature is mentioned with its possible causes on pp. 121 and 124. A third case, a quarryman aged 45, was unable to work because of ataxia. Among multiple signs, including W.R. + in both serum and cerebrospinal fluid, was coldness and congestion of the left foot. He was relieved by a long course of treatment, and has now been at full work for over six years.

I have never seen persistent cold congestion of the feet except in these three syphilitics. All were clinically cured by specific treatment.

CHAPTER XII

ON CERTAIN TYPES OF TONGUE AND THEIR RELATION TO SYPHILIS

THE two opinions which appear below, given to the writer respectively by a professor of surgery and a teacher in a London medical school, are sufficient at least to show that the interpretation of signs found in the tongue is a matter on which there is no uniform opinion.

The professor of surgery writes: "What I have tried to teach my students is that linear scars of all kinds are probably the result of syphilis—that if the scars are multiple and like a fern leaf, the probability almost becomes a certainty. If in addition the papillæ are smoothed or ironed out, i.e., if the roughness is replaced by a smooth track or even by a leucoplakic patch, then syphilis is certain."

The teacher of medicine says: "The only form of glossitis which we know to be syphilitic is the interstitial variety."

The opinion of the former was that signs of syphilis were to be sought for in the tongue; the latter believed that no reliance was to be placed on the signs in this organ.

This is no place to introduce so large and well-explored a field as the pathology of syphilis. Warthin

believed that clinicians in general do not know the pathology well enough to recognize clinical signs in the so-called latent period. However true that may be, it is certainly true that a sound knowledge of the reactions of the body to the spirochæte is of great importance and provides a formula which may be applied to many obscure conditions. Sir James Mackenzie called attention to the difficulty which general practitioners found in making a diagnosis in those cases which did not conform to the well-defined types which they had met in hospital.

I have found that if tongues similar to those of this series are seen in routine examination, then it is necessary to exclude syphilis by direct examination, and, further, that for this purpose the Wassermann reaction is useless, giving an almost uniformly negative result.

For descriptive purposes these tongues may be divided into five classes.

Type 1.—Hypertrophic indented, shows deep sulci when protruded. There is general hypertrophy of papillæ. In this series, this type has usually been found in young adults. Colour normal.

Type 2.—The surface presents a uniform mosaic of small, more or less square areas. Furrows well marked but no shedding of epithelium. Size, colour, and mobility normal.

Type 3.—Resembles *Type* 1 in the nature of sulci, but the parts between the sulci are smooth and the colour is pinker, with a suggestion of a thin film of skim-milk on the surface.

Type 4.—The whole tongue is drier, smoother, and firmer. The fissures appear more fibrotic and tend to be rectangular. The organ is smaller than normal and deep fibrosis limits mobility.

Type 5.—Smooth, pale atrophic surface with patches of leucoplakia and occasional fissures. This type is not easy to illustrate by photography as there is little contrast except to the naked eye.

TYPE 1: SULCATED OR FERN-LEAF

Jonathan Hutchinson describes this as the sulcated or fern-leaf tongue. He believed it was due to inflammation in infancy, e.g., thrush, and stated that it had no connection with hereditary syphilis.

Stellwagon and Gaskill[1] say it is the result of irritating influences and various forms of glossitis and other diseases, some of which may be due to syphilis either acquired or hereditary.

Sutton[2] says, " aside from the cases which develop as the result of heredity, glossitis of syphilitic or other origin is the most frequent causative factor ".

Spencer and Cade[3] say that lingua plicata is familial and of no importance.

I have seen this type of tongue in 7 patients; in 2 found accidentally there was no discomfort and no sign of general disease. The remainder suffered as follows :—

Case 1 (*Fig.* 10).—Female, aged 24. Complains of chronic nasal catarrh and cough. Congestion of both bases. Cleared up under vaccine treatment. Finger-nails and toe-nails narrow, thick, yellow, and opaque, no cuticle—the ' horn ' type of Jonathan

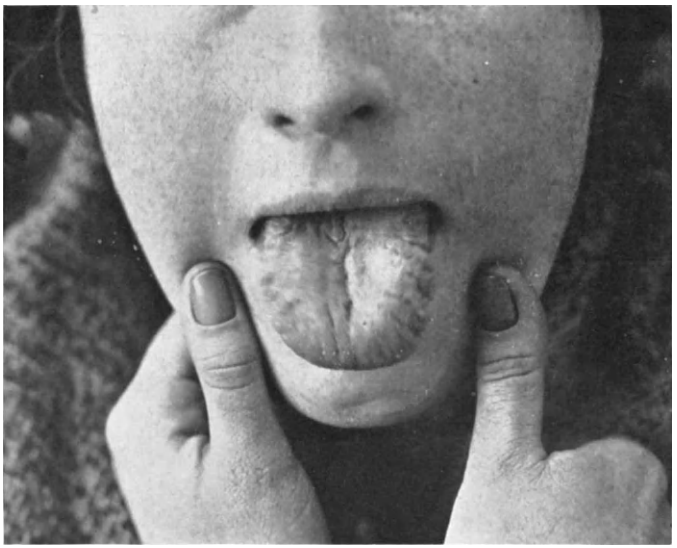

FIG. 10.—*Case* 1, *Type* 1. Sulcated or fern-leaf tongue.

Hutchinson. Her mother and brother are inmates of mental hospital. Serum W.R., 1 M.H.D.

Case 2.—Female, aged 35. Complains of sore tongue, fears cancer. Mouth waters. Teeth always on edge. Indigestion, flatulence, and acidity not related to food. Mild hyperthyroid type. W.R. negative. The tongue has remained *in statu quo* for six years. The patient's mother is one of eleven children, of whom six died in infancy. One brother died at 45 of 'fatty heart'. She has the same type of indigestion as her daughter, and says her father suffered similarly. She also has a perforated nasal septum, and is subject to precordial pain. A crippling attack of polyarthritis was cured by mercury and iodides. Serum W.R., 1 M.H.D.

Case 3.—Male, aged 25. For twelve months suffered from epigastric and hypogastric pain. There was also headache and deafness and some alteration in character in that he was more nervous and retiring than formerly. In routine hospital examination W.R. + in all dilution was found in the cerebrospinal fluid. He was relieved by specific treatment and has remained well since (three years). An additional feature of interest was persistent blueness and congestion of the feet and legs even when the patient was in bed. He did not feel discomfort, and this sign disappeared during his convalescence.

Case 4.—Male, aged 26. Hyperthyroid, complaining of precordial discomfort and sensations of suffocations after exertion. Unequally reacting pupils. No physical signs of lues. Apparently relieved by bismuth injections and returned to work. Four months' symptomatic treatment had failed to relieve. W.R. +.

Case 5.—Both patient and his father and two aunts have W.R. +.

The associated conditions are noteworthy :—

Case 1.—(1) Family history of mental disease. (2) Horny nails. These are mentioned by Hutchinson, Sutton, et al., but little is known of the pathology, most that is written being guess-work. Some cases, however, are acknowledged to be due to syphilis.

Case 2.—Perforated nasal septum and anginal attacks and response to specific treatment in mother.

Case 3.—(1) W.R. + in cerebrospinal fluid. (2) Passive congestion of feet and legs. Of two other patients in whom I have seen this condition one is No. 5 illustrating *Type* 5 (*Fig.* 17, p. 124),

where particulars are given. Jonathan Hutchinson also noted the association of the two conditions, but apparently offered no explanation.

Case 4.—Therapeutic response after failure of symptomatic treatment; this therapeutic feature was present in all the cases in this group.

TYPE 2: LINGUA SCROTALIS

Case 1 (*Fig.* 11).—Male, aged 50. Crippled by arthritis deformans which began four years ago. Chronic myocarditis. One sister is totally blind from chronic plastic iridocyclitis; another has choroidal atrophy with W.R. +.

Case 2.—Male, aged 70. Post-herpetic neuralgia, arteriosclerosis, cyanosis, miosis. Was bedridden for fifteen months. After three months' treatment with mercury and iodides he was able to get about, superintend his farm, attend sales, etc., and has continued to do so for four years.

Case 3.—Female, aged 70. Sciatica for four years. Auricular fibrillation. Died after six months' epigastric pain and vomit of frothy mucus. Carcinoma suspected, but none found at autopsy. Heart showed diffuse fibrosis. Of eight children, four died in infancy and two survivors have facies of congenital syphilitics. There was, in addition, one miscarriage.

TYPE 3

Case 1 (*Fig.* 12).—Male, aged 64. Complains of shortness of breath on exertion four or five years. Is awakened by attacks of dyspnœa at 3 a.m. each morning. Has been treated for asthma. Worries over trifles. Married—no children, one miscarriage and twins died at birth. Family history negative. B.P. 200/100, booming second aortic sound.

During treatment with bismuth, mercury, and iodides he developed persistent headache, which was worse when he stooped. This gradually improved. Six weeks after onset of treatment had an attack of unconsciousness in which he fell down in the street and remained unconscious for ten minutes.

Henry Head taught that these attacks occurring suddenly and without warning in middle life were evidence of one of four things: early G.P.I., cerebral syphilis, alcohol, or cerebral tumour. The last two could be ruled out in this case. The response to therapy was satisfactory.

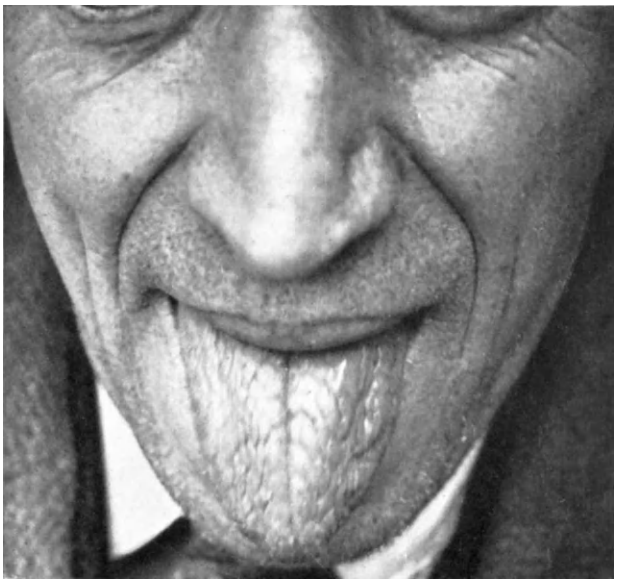

FIG. 11.—*Case* 1, *Type* 2. Lingua scrotalis.

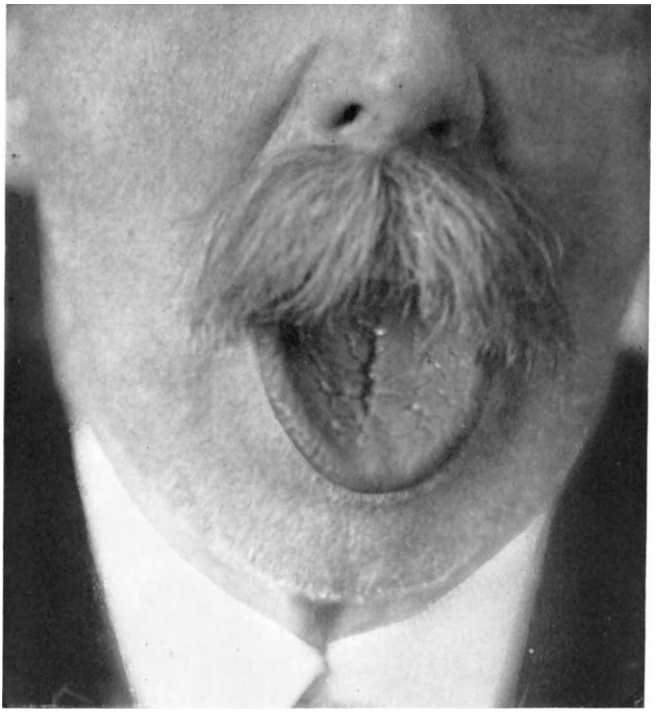

FIG. 12.—*Case* 1, *Type* 3.

FIG. 13.—*Case* 1, *Type* 4.

Case 2.—Female, aged 58. Has been bedridden for four years, and finally admitted to a mental hospital. Diagnosis of menopausal neurasthenia supported by consultant, and this the writer failed to dislodge. Complains of vague pains, depression, and weakness; fears cancer and tuberculosis. Latterly has a fixed idea that she is about to die of phthisis. On examination she has unequally reacting pupils, hyposensitive ulnar nerve trunks, and absent knee-jerks. Long-standing moist fissures at angles of mouth. Low pyrexia for months at a time. B.P. variable, 150/90 to 190/100. Cerebrospinal fluid under tension, 0·3/1000 protein, 5 lymphocytes per c.mm. W.R., 1 M.H.D. Serum W.R., 1 M.H.D.

The husband's family history is arresting. Two of his sisters, two brothers-in-law, and a nephew have either W.R. + or other evidence of syphilis.

TYPE 4

Case 1 (*Fig.* 13).—Male, aged 70. Dysuria with retention and diverticula of bladder. No stricture, no enlarged prostate. The tongue and unequally reacting pupils were the only features suggesting lues and led to the discovery of W.R. ++. The general condition was much improved by specific treatment and suprapubic cystotomy.

Case 2 (*Fig.* 14).—Female, aged 65. Heart attack resembling coronary thrombosis followed by a period which clinically resembled uræmia but without evidence in blood or urine. Apathetic, with short periods of unconsciousness, dry tongue, muddy complexion. W.R. ±. Healthy children. Beyond unequally reacting pupils, chronic varicose ulcers, and large scars over elbows and knees, there was no other feature suggesting syphilis. Reacted well to treatment and for the last five years has been able to do all her own housework.

TYPE 5

Cases 1 and 2 are sisters and are transitional in that they show features common to both *Types* 4 and 5.

Case 1.—Female, aged 63. Wasting of right forearm and hand for two years. Abductors of thumb completely wasted, remaining muscles partially atrophied. Ulnar nerve trunk anæsthesia. Husband died twenty-five years ago of locomotor ataxia. No miscarriages, and children all appear healthy. W.R.++. Wasting was arrested by specific treatment.

Case 2.—Female, aged 60. ' Attacks ' resembling petit mal with vertigo of recent onset, unequally reacting pupils, anæsthesia of ulnar nerve trunks. W.R.±. No other sign of syphilis. Cerebrospinal fluid normal.

Response to specific treatment was slow, but gave more satisfactory results than symptomatic therapy. Husband underwent amputation through the thigh for gangrene of foot due to popliteal endarteritis.

She has now been symptom-free for three years.

The brother of these two patients had a tongue of *Type* 4, absent knee-jerks, no abdominal reflex on left, normal on right, unequally reacting pupils, palpable spleen, and fibrinous pericarditis. Serum W.R., 2 M.H.D. He eventually died of pulmonary phthisis.

Case 3 (*Fig.* 15).—Female, aged 61. Spasmodic dysphagia for many years. W.R. —. Has remained well for three years after a course of bismuth injections combined with mercury and iodides.

Case 4 (*Fig.* 16).—Male, aged 60. Vertigo, palpitation, vague paræsthesia in head. Had been unable to work for six months. W.R. —, and no physical sign of syphilis except miosis with irregularity of outline of the left pupil. He was completely relieved by six weeks' antisyphilitic treatment and was well and working two years later.

Case 5 (*Fig.* 17).—Male, aged 60. For four years had been unable to work owing to pains in the legs. The legs and feet were blue and congested. Bilateral pes cavus. Wife had two miscarriages, and one other child. W.R. negative in serum and cerebrospinal fluid. The tongue was the only evidence of syphilis beyond the general appearance of ill health. He became fit for work after three months' treatment and has remained so during the intervening two years.

The blueness and congestion of the lower extremities noted in this case and in *Case* 3, *Type* 1, is evidence

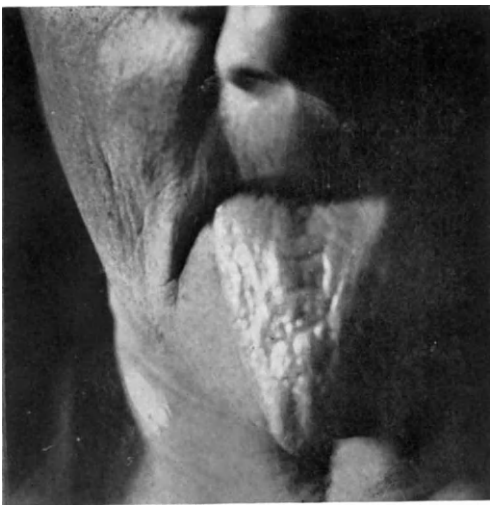

FIG. 14.—*Case* 2, *Type* 4.

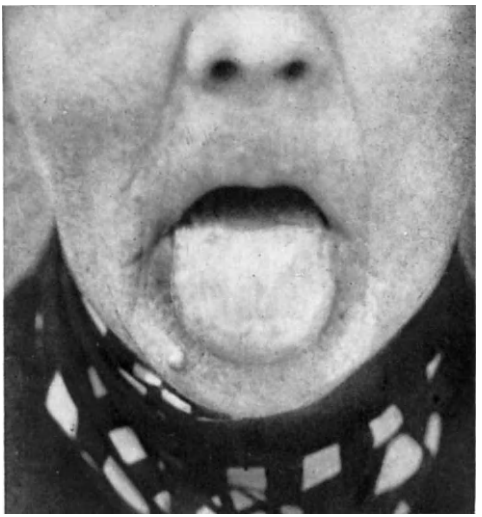

FIG. 15.—*Case* 3, *Type* 5.

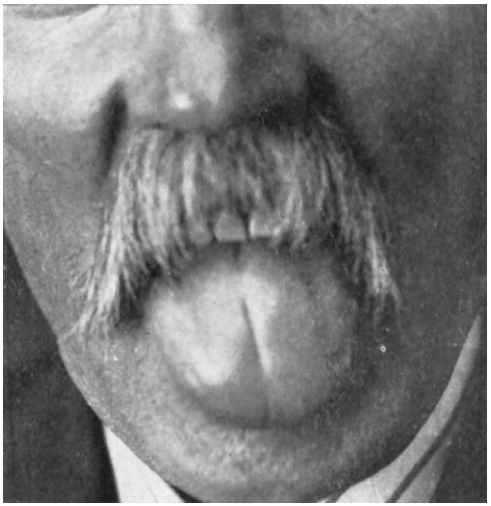

FIG. 16.—*Case* 4, *Type* 5.

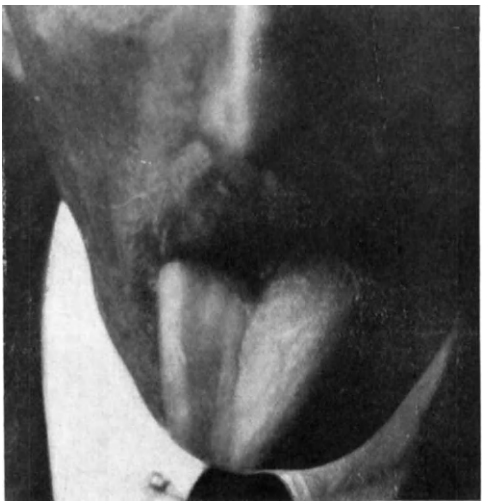

FIG. 17.—*Case* 5, *Type* 5.

of disorder of the peri-arterial sympathetic nerves. The pathology of syphilis, a primary lymphatic disease, invading the vessel wall from without, makes direct exclusion of spirochætosis imperative when these signs are found. For this, the simple performance of the Wassermann test has been found to be inadequate.

GENERAL CONCLUSIONS

In the foregoing an attempt has been made to describe *types* of tongue; there can be no exact description of so variable a condition as the syphilitic tongue, just as it is most difficult to describe the protean symptoms of the disease.

The tongue is the organ most readily examined, and the discovery of hypertrophy or atrophy resembling that shown here should lead to direct examination for syphilis. In the absence of other evidence, it justifies the exhibition of bismuth, mercury, and iodides in any baffling symptom-complex, for it is the business of the family doctor to relieve his patient's symptoms, and experience has taught the writer that no diagnosis is more often missed than latent syphilis.

The reliance on the Wassermann test is deplorable. The following extracts are from a few of the many authors who have emphasized the inadequacy of the blood-test.

1. " Congenital syphilis in adults may be expected to give a negative Wassermann reaction."[4]

2. " In congenital syphilitics the Wassermann reaction tends to die out as they grow up, so that

adolescents and young adults may show a negative reaction."[5]

3. " A very large proportion of the late latent cases of syphilis give a negative Wassermann reaction even in the presence of active lesions."[6]

It is not too much to say that the Wassermann test has become master instead of servant, and that its failure to show a positive reaction in the large group of syphilitics indicated in the foregoing has led to much confused thinking and to laboured efforts to explain the clinical features with non-syphilitic pathology.

REFERENCES

[1] STELLWAGON and GASKILL, *Diseases of Skin*, 1923, 9th ed., 1270.
[2] SUTTON, *Diseases of Skin*, 7th ed., ii, 1342.
[3] SPENCER and CADE, *Diseases of the Tongue*, 1931, 185.
[4] OSMOND, *Interpretations of Aids to Diagnosis*, 351.
[5] OSMOND, *Ibid.*, 356.
[6] WARTHIN, " Cardiovascular Syphilis ", *Atlantic Jour. Med.*, 1927, Aug.

CHAPTER XIII

CANCER AND SYPHILIS

A DISCUSSION AND AN EXPERIMENT

It is recognized that cancer may arise in a syphilitic scar. There are many records of isolated cases such as that in the *Cancer Review*, 1929 (p. 216): "Histological examination of the removed tumour showed clearly that the cancer had arisen in an old gummatous ulcer (of the epiglottis)." Some authors go a step further and maintain that syphilis is the precancerous condition in certain organs, notably the tongue, cervix uteri, and breast. In cancer of the tongue percentages of positive Wassermann reactions vary from 29 (Belote)[1] to 80 (Romanis and Mitchiner). In cancer of the cervix uteri Touraine[2] quotes Audry, who concluded that one half of these cancers had a syphilitic beginning. Suquet found 68 per cent of them luetic. Bertrand obtained positive Wassermann reactions in 68·5 per cent. Touraine himself believes that there has been syphilitic infection in at least two-thirds of these cancers, the specific lesion forming a precancerous site as may occur at other mucous orifices. In cancer of the vulva Belote found W.R. + in 11·8 per cent. Again, when investigating cancer of the breast, Hirzfeld and Haller[3] have found positive W.R.

in 20 per cent. Verotti[4] says that 9 out of 11 of his cases were syphilitic.

The foregoing are records of observed facts. If they are accepted and applied with a knowledge of the pathology of syphilis, certain logical conclusions are inevitable. After inoculation spirochætes are quickly and widely distributed by the lymphatics and cause pathological changes in many parts of the body; if therefore syphilis is a precancerous state in the organs mentioned, it will play a similar role in organs not so easily examined. There is no escape from this conclusion.

As a further step we may now reflect on the theories of Sampson Handley and of Cherry on carcinogenesis. Handley[5] says that the first step is proliferation of the endothelium of lymphatics, followed by blockage of the lumen, lymph stasis, and finally metaplasia of the affected cells. He says: "It is significant that the lymphophilic organisms of tubercle and syphilis are those most clearly incriminated as connected with the production of cancer, and it is rather strange, in view of the close study which has been devoted to syphilis, that the disease has never been identified as essentially a lymphangitis."

Cherry[6] has defined cancer as "in most cases the expression of the resistance of the cells to a second or subsequent invasion by the *Bacillus tuberculosis*." He seems to have proved experimentally in mice that inoculation with tubercle bacilli disposes to cancer, for in 349 mice so inoculated cancer developed in 80, whereas in 305 control mice cancer developed in 9,

giving a percentage incidence of 23 and 3 respectively. He noted that these tumours exhibit no uniformity in site or type—that is to say, various tumours occurred in various sites. His main conclusion is that conditions where lymphocytic infiltration is characteristic are more prone to undergo malignant change, and he argues that the lymphocytes take an active share in the production of malignant disease, and are an essential link between the mouse and the malignant cell. Although he does not specifically mention lymph stasis, there is a strong parallel between his work and Handley's.

It may prove to be as difficult to apply the facts of mouse cancer to the human disease as it has been to apply those of fowl sarcoma, and at the outset this criticism may be made. In man generalized tuberculosis is, as a rule, fatal, and the arrested stage is marked by static calcification rather than by chronic proliferation. On the other hand, generalized syphilis is seldom fatal, and the arrested stage is marked, not by calcification but by chronic adenitis in unstable equilibrium. On general principles the essential precancerous lymph stasis is more likely to occur in syphilis than in tubercle.

Handley[7] also makes this important statement: "As soon as the chronic irritant has produced permanent obliteration of the local lymphatic vessels in the precancerous area, it has done its work. From this moment the removal of the chronic irritant will fail to arrest the evolution of cancer years afterwards."

There is now little doubt that syphilis is a lymphophilic disease. Within a few hours of inoculation the virus is found in neighbouring lymphatic glands. At the end of the secondary stage it is swept up into the main lymphatic groups. The work of Martland, Klotz, Coombs, and others has established this point. They say : " [Spirochætes] pass by lymphatics to the peribronchial and mediastinal glands, which become reservoirs for the storage of spirochætes " (Martland). " It is from two main lymphatic drainage beds—the thoracic and the abdominal—that the syphilitic virus comes to be distributed " (Klotz). " The cellular infiltrations that are the distinctive mark of syphilis well out of the mediastinal lymphatics " (Coombs).

Why, then, is the relation of syphilis to cancer not recognized more generally ? Among the important reasons are :—

1. Too narrow a definition of syphilis. The word is confined to the stages of the disease when spirochætes are demonstrable, the Wassermann reaction positive, or where there are pathognomonic signs. The whole fields of congenital, parasyphilis, and latent syphilis are ignored.

2. Too easy acceptance of the conclusions of those cancer research workers who have attempted to correlate the two diseases by seeking evidence of syphilis only in serological tests.

3. Widespread neglect of the study of latent syphilis and the subjection of clinical opinion to the Wassermann test. Warthin says : " Undoubtedly the clinician of to-day has lost much skill in the diagnosis

of syphilis. He does not know the pathology of the disease well enough to be always vigilant for its protean manifestations, and especially because he has come to depend on one thing—the laboratory report of a negative or positive Wassermann reaction."

That this opinion is not an over-statement is shown by the paper of Moore and his collaborators,[8] which reveals that out of 105 cases of syphilitic aortitis admitted to the Johns Hopkins Hospital and demonstrated at autopsy, only 4 had been diagnosed in the wards at the hospital! This is truly a remarkable state of affairs in one of the foremost teaching hospitals of the world!

A paper by Fry[9] on this subject has been freely quoted and its conclusions apparently accepted without comment. His object was "to ascertain the relation of syphilis to malignant disease as determined by the Wassermann reaction." His conclusion was, "In general, from the above figures, there is no evidence that syphilis plays any direct or important part in the production of cancer." There is an obvious fallacy in making the positive Wassermann reaction synonymous with the presence of the disease syphilis, and the conclusion reached must therefore be incorrect.

The inadequacy of the Wassermann reaction as a diagnostic standard has been exposed so often that it is both surprising and regrettable to find it retaining a deciding value in any investigation such as Fry's, and especially that the conclusions based on it should be accepted without comment.

Kolmer[10] (1923), in a series of 363 cases of latent syphilis, found a positive reaction in only 40 to 48 per cent, the higher percentage being in the earlier stages. At the League of Nations Laboratory Conference in 1928, the Wassermann test was compared with certain flocculation tests. In 496 cases of syphilis a positive result was found in 208 only, and it is patent that for the purposes of this investigation no doubt as to the diagnosis was permissible. This was confirmed at the Montevideo Conference, 1931. Again, it is well known that a negative Wassermann reaction is the rule in congenital lues after puberty. When Farquhar Buzzard[11] (1921) said that his faith in the Wassermann test as a diagnostic standard had been shattered, he expressed the only possible rational opinion.

As suggested above, it is logically incorrect to correlate cancer and the florid stage of syphilis with positive serum while ignoring the latent stage with negative serum. It is more than incorrect, it is deceptive, because Cherry has shown in the case of tubercle that the leucocytosis of florid phthisis is antagonistic to cancer, but that the lymphocytosis of the chronic disease predisposes to malignant change. Precisely parallel histological conditions occur in syphilis.[12] In acute exacerbations the infiltrations are composed of polynuclear cells, the latent period is characterized by mononuclear lymphocytosis.

If Cherry is right (in saying that leucocytosis and florid phthisis are antagonistic to cancer and that the precancerous condition is chronic lymphocytosis), it

may explain why the relation of cancer to syphilis has not yet been established, because hitherto only the obvious, clinical, and serologically positive stage of syphilis has been used in this connection, and this, by analogy with tubercle, should be antagonistic to cancer. It is clear that the latent disease deserves investigation.

After being interested in latent syphilis for a number of years the writer came to believe that cancer is a common termination of the disease. Repeated association of the two conditions (*see Appendix A*) led to an attempt : (1) To establish evidence of both diseases in a consecutive series of cases ; and (2) To investigate a remarkable cancer family for evidence of chronic lues.

THE CANCER FAMILY

Husband and wife both died of cancer of the stomach. They had ten children, of whom six reached adult life. Five of the six have died of cancer of the stomach and there is one survivor. In none was a post-mortem examination permitted, but in three a filling defect was shown by X rays, and in all the clinical course was typical. One male had in addition an epithelioma of the angle of the nose treated by local excision.

The full significance of this family history was not realized until too late, and efforts to trace a precancerous condition possibly common to all were directed to the surviving husbands and wives.

Case 1.—Male. Carcinoma of stomach and epithelioma of nose.
Wife.—No pregnancy.

1923.—Abdominal pain and nausea. Lump in left hypochondrium. Improved under symptomatic treatment.

1926.—Anorexia, cough, insomnia. Cervix uteri boggy and cystic. Improved under symptomatic treatment and chemical cautery to cervix.

1927.—Same complaint. Noted: "nil to be found anywhere except lump left hypochondrium and basal congestion." Lump again noted the following month. Attacks of coughing and vomiting continued with low pyrexia. Repeated examination for T.B. negative. Noted: "looks like cancer but gets better."

1928.—Sibilant râles left apex. B.P. 170/180. Trace of albumin.

1929.—Months of coughing with temperature of 99°. Dyspnœa, fatigue, B.P. 170. Sputum examination negative several times.

1930.—Serum W.R., 1 M.H.D. C.S.F. 0·37/1000 globulin, 10 lymphocytes per c.mm. Fluid otherwise normal. Patient able to get about. Mercury and iodides administered. A general improvement in health has been maintained to the time of writing (October, 1936).

Case 2.—Male. Carcinoma of stomach.

Wife.—

1923.—Giddiness and heartburn. B.P. 200. Chronic middle-ear deafness. Unequally reacting pupils.

1925–7.—Intermittent treatment for cardiac arrhythmia and high blood-pressure. Inequality of pupils noted several times.

1930.—Loss of memory. Keeps a shop, and cannot remember an order given few minutes earlier. Cannot say who has paid money. Pulse 138. Resting B.P. 180/112. Serum W.R., 1 M.H.D. C.S.F. 0·5/1000 globulin, 7 lymphocytes per c.mm. Otherwise normal.

1931.—Gradually went downhill and died of left ventricular failure with normal rhythm. Successive records of blood-pressure: 148/80, 116/70, 150/86, 170/100, 140/90, 150/80. There were intermittent attacks of arrhythmia, but no bruit.

Only child died of phthisis at 26.

AUTOPSY (Report by Pathological Institute, Charing Cross Hospital).—

Liver.—Fine multilobular cirrhosis. Patchy infiltration of fibrotic areas with small round cells and plasma cells. Arteries show sclerotic thickening of walls and slight endarterial change.

Spleen.—Fibrosis of stroma. Arterial sclerosis and endarteritis. Fibrosis round larger veins.

Pancreas.—Diffuse fibrosis and marked arteriosclerosis.

Heart.—Chronic interstitial myocarditis.

Case 3.—Male. Carcinoma of stomach.

Wife.—Unequally reacting pupils. Subject to attacks of lumbar pain, paroxysmal, relieved only by morphia. No evidence of calculus. Serum W.R. negative. C.S.F. 0·55/1000 protein, 7 lymphocytes per c.mm. Fair decrease in glucose. Otherwise normal.

Case 4.—Female. Carcinoma of stomach.

Husband.—Died of acute meningitis, said to be influenzal; remainder of family history also negative.

Case 5.—Female. Carcinoma of stomach.

Husband.—Has chronic pharyngo-laryngitis, and myocardial debility with aortic systolic bruit. Serum W.R., 2 M.H.D.

Eldest son is a mental defective, one daughter has nervous dysphagia, remaining children healthy.

Surviving Daughter.—Since 1918 has had intermittent abdominal pain, dyspnœa, palpitation, and enlarged spleen. Adherent kinked appendix removed with partial relief. Has been kept on Hutchinson's pill for two years with benefit.

Husband.—Unable to work since 1925 on account of myocardial insufficiency, dyspnœa, epigastric pain, and arrhythmia.

1926.—Heart enlarged, electrocardiogram shows relative left ventricular hypertrophy. Signs of perihepatitis.

1930.—Arrhythmia, dyspnœa, unequally reacting pupils. Serum W.R., 1 M.H.D. Children healthy.

1936.—Has done light work continuously since. Mercury and iodides administered throughout.

The relation between cancer and latent syphilis in the foregoing notes will not at first be apparent. But a student of the latter disease will say that the notes as a whole consistently suggest that such a relation exists, and that a more exact inquiry is called for. Such an inquiry was therefore attempted, with the under-mentioned result.

During the course of one year all cancers were examined microscopically and the patients specially examined for syphilis. There were 20 cases and they fell into three groups: *Group I*, evidence of both diseases clear; *Group II*, evidence of cancer with latent syphilis diagnosable on other grounds than positive Wassermann reaction, demonstration of spirochætes, or pathognomonic lesions; *Group III*, evidence of cancer, but no evidence of syphilis.

Out of the 20 cases, 12 fell into *Groups I* and *II*, a result which supported pre-existing opinion and which was to be expected from the observations and theories mentioned in the opening pages.

GROUP I

CASES WITH BOTH MALIGNANT DISEASE AND SYPHILIS

Case 1.—Male. Carcinoma of liver. Unequal Argyll-Robertson pupils. Absent knee-jerks. Coronary thrombosis. Many miscarriages in wife and no living children. W.R. negative.

Case 2.—Female. Carcinoma of breast. Microscopical evidence of syphilitic aortitis. W.R. negative.

Case 3.—Female. Carcinoma of breast. W.R. positive. Diagnosis of syphilis confirmed during stay in a Teaching Hospital.

Case 4.—Female. Carcinoma of œsophagus. Wife of a syphilitic. Smooth pale area on either side of tongue. Knee-jerks feeble. Ankle-jerks absent. Plantar response extensor on both sides. Microscopical evidence of syphilitic aortitis. W.R. negative.

Case 5.—Female. Carcinoma of small intestine. W.R. positive (serum). C.S.F. 1/1000 protein, 6 lymphocytes per c.mm. W.R. positive (C.S.F.).

Case 6.—Female. Carcinoma of rectum. W.R. negative. Multiple post-mortem evidence of syphilis unsuspected during life.

It is noteworthy that four of the foregoing cases had a negative Wassermann reaction (method No. 1 of Medical Research Council).

GROUP II

Cases of Malignant Disease with Circumstantial Evidence of Syphilis

Case 1.—Male. Carcinoma of stomach. Fibrosis and lymphocytic infiltration of both heart and liver. Wife is anæmic, has unequal pupils, and smooth atrophic tongue. There were two children and two miscarriages. W.R. not done.

Case 2.—Male. Carcinoma of rectum. Unequal pupils, paræsthesia legs. Responded to antisyphilitic treatment before onset of malignancy. No children. Evidence of lues in several members of the wife's family. W.R. negative. Localized lymphocytic infiltrations in all organs examined post mortem.

Case 3.—Female. Carcinoma of œsophagus. W.R., 1 M.H.D. Lymphocytic infiltration about vasa vasorum of aorta. Minor clinical signs of latent lues in self and good response to therapy in hu band. No children.

Case 4.—Female. Carcinoma of œsophagus. Long-standing anæmia. Atrophic tongue, moist fissures angles of mouth. W.R., 1 M.H.D. C.S.F. 0·3/1000 protein. Positive therapeutic test before onset of malignancy. Post mortem : fibrosis and cellular infiltrations in several organs on which a pathologist reported " definitely pathological and could be syphilitic ".

Case 5.—Female. Carcinoma of stomach. Hemiplegia of eight years' standing. Tongue red and glazed. One brother died of carcinoma of stomach, another of ruptured aortic aneurysm. Post mortem : localized perivascular infiltrations in liver and kidney.

Case 6.—Female. Cancer of breast, 1921 ; cancer of uterus, 1929. Both confirmed by microscopy. Unequal pupils. W.R., 1 M.H.D. Post mortem : aorta, liver, and pancreas show localized perivascular infiltrations of lymphocytes. The husband of this patient was one of four married brothers. No children of any marriage. One wife died of carcinoma of the stomach, another was found dead in bed. The remaining wife is healthy, but her husband has chronic intractable headache.

GROUP II

CASES OF MALIGNANT DISEASE WITHOUT EVIDENCE OF SYPHILIS

Case 1.—Male. Carcinoma of lung. Slight cellular fibrosis in heart and liver.

Case 2.—Female. Carcinoma of uterus. Fatty cirrhotic liver. Pathologist's comment : " I cannot say that this is syphilitic."

Cases 3–8.—Similar negative reports.

It is a matter of experience, supported by the foregoing observations, that syphilis in man is a common precancerous state—so common that the spirochæte should at least rank with shale oil, etc., as a recognized cancer-producing irritant, and much more important because of its wide distribution. Shale-oil cancer is banished by prohibiting the use of the irritant ; it is possible that the incidence of cancer in general could be diminished by the proper treatment of latent lues.

Many workers engaged in experimental cancer production in animals, and observers of occupational cancer in man, have stressed individual susceptibility. The majority of mule-spinners, for example, remain cancer-free, the minority are more susceptible and develop cancer. It might be profitable to examine the latter for microscopical evidence of syphilis rather than to rely solely on the Wassermann test.

Exact experiment is impossible in the human subject. It is said that 70 to 80 per cent of human autopsies will reveal healed tubercle. In Vienna it is taught that tubercle bacilli can be cultivated from 70 per cent of bloods taken at random (Lowenstein). Such facts destroy the possibility of exact experiment.

Some critic may hold that all the lymphocytic infiltrations mentioned here are tuberculous, and it would be difficult to prove the contrary, but experience and the therapeutic test remain to support the belief that the infiltrations are syphilitic.

" Abrupt classification is a hindrance to sound perception of clinical truth " (Hutchinson). It may be that the study of latent syphilis is neglected because abrupt classification and clear definition of its signs are so difficult. Even Hutchinson could only speak of " conditions due to syphilis but not syphilis ", and Osler and Andrewes describe chronic inflammations found in syphilitics but not in themselves specific. At the present time we must accept the fact that the signs of latent syphilis and the microscopical diagnostic standards of Warthin are disregarded, and that clinical opinion is in subjection to the Wassermann test.

Circumstantial evidence is found in the statistics of the Registrar-General and of the Medical Research Council's inquiry into occupational cancer. A correlation is established between cancer of the tongue, cirrhosis of the liver, and cancer of the œsophagus. There is also an agreed but unexplained correlation between syphilis and carcinoma of the œsophagus. The relation between cancer in the tongue and syphilis has already been mentioned. With regard to syphilis, cirrhosis, and cancer of the liver, Holmes[13] (1931) ignores the correlation with syphilis and discusses only that with alcohol. She concludes that " the evidence makes it extremely probable that alcoholism is partly

responsible for cancer in these organs (liver, tongue, œsophagus, and stomach) ". This conclusion is based on the statement that " in this country cirrhosis of the liver is practically always due to chronic alcoholism.". It is true that alcohol is accepted as the cause of cirrhosis of the liver, but it is also true that its position is more due to tradition than to demonstration. When heavy drinking was universal and cirrhosis common, it was not unnatural to associate the two, but efforts to produce cirrhosis in animals with concentrations of alcohol comparable to those ingested by man have not afforded satisfactory evidence. On the other hand, we now know that syphilis was and is extremely prevalent and that every established syphilitic, whether congenital or acquired, has some degree of perivascular infiltration of the liver, and that this may vary from slight plasma-celled infiltration of the periportal tissue to the most marked cirrhosis. Spirochætes are demonstrable in large numbers in the livers of congenital syphilitics, and cirrhosis in later life is inevitable in all cases which survive. As long, however, as the microscopical diagnostic standards of Warthin remain unaccepted, so long will alcohol retain its leading position in the etiology of cirrhosis.

On another page Holmes (1931) says: " On the whole the most generally accepted belief at the moment, and one which has convincing figures from Sumatra and Calcutta to support it, is that liver cancer supervenes on cirrhosis of the liver—which is a common disease among the natives. In Sumatra a

very large percentage occurs in definitely cirrhotic livers." Mohammedans abstain from alcohol, but they share the liability to cirrhosis and carcinoma, and no hypothesis can be true unless it is applicable to all the known facts.

The difficulty in proving a direct connection between cancer and syphilis lies in the obscurity into which congenital and latent syphilitics gradually recede as the infection becomes less and less virulent; but the difficulty can be overcome by deduction from the facts of pathology and clinical observation. An individual once infected with spirochæte, congenitally or otherwise, has for ever a chronic lymphangitis with potential lymph stasis, and also multiple foci of chronic inflammation in some of which active tissue proliferation persists. He has, in short, the factors necessary for cancer production.

It is unfortunate that hospital staffs are unable to watch patients for many years, and that they are thus compelled to build up family histories from what the patient tells them and not from their own observations, otherwise the relation between cancer and syphilis would not remain unestablished.

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CHAPTER XIV

CHRONIC PAINFUL SUPERFICIAL ULCERATION OF THE MOUTH AND PHARYNX

THIS is a rare condition which is characterized by the presence of irregularly shaped superficial ulcers of the buccal mucous membrane and pharynx. The surface is covered with a yellowish thin membrane. Great chronicity is the rule, and widespread scarring shows the site of former ulcers. Pain is very severe and seriously interferes with eating.

Case 1.—This was a medical colleague aged 60. She complained of painful ulcers of the mouth all her life and persistent hawking of mucus from the throat. At the time of examination there were eight ulcers of the palate and vestibule extremely tender to touch. She habitually used an analgesic mouth-wash before each meal, and the pain in the mouth materially interfered with sleep.

She showed none of the signs or symptoms usually associated with syphilis, but gave an interesting family history.

Father: Died at 78 of cancer of the larynx. Was a chronic asthmatic.

Mother: Died at 81 of heart failure.

Brothers: One alive and well. One dead of typhoid.

Sisters: One alive and well, one died of whooping-cough at six weeks. One—the next older than herself—is a chronic asthmatic and bronchitic, and has hazy corneæ, the result of chronic inflammation when she was 14 years of age. The only child of this sister has diabetes.

Patient's husband died of cerebral sclerosis in the forties. The first child died at 9 days of convulsions. It had a perforating ulcer on the soft palate. The only other child appears perfectly healthy, but is the victim of severe hay fever.

The patient volunteered that during the two pregnancies the ulcers cleared up entirely.

This patient had sought relief in many places, including two medical schools. Usually the ulcers were regarded as secondary to gastric or hepatic disorder. She had never received any relief, and local applications such as silver nitrate were too painful to be contemplated. The possibility of syphilis was never suggested ; even her own expressed suspicions were dismissed as impossible.

Treatment consisted of a course of intravenous stabilarsan and intramuscular bismuth with Sanitas as a mouth-wash. Because of the favourable effect of pregnancy, corpus luteum and placenta were given in addition. The effect of this treatment—ignoring the negative Wassermann reaction—is best described in her own words : " I have been quite free of the ulcers and have had no clearing of my throat. It is so wonderful being able to eat and talk without pain such as I have had for about eight years."

Case 2.—Shop assistant, aged 33. For six years has had crops of very painful ulcers in the mouth and has found nothing to relieve them.

ON EXAMINATION.—Multiple shallow ulcers of the mouth and palate up to $\frac{1}{4}$ in. diameter. Extensive superficial scarring of palate. Thin type, no abnormal physical sign found on examination except enlarged epitrochlear and axillary glands. Family history negative —two healthy children and no miscarriages.

Cured by a six weeks' course of intravenous stabilarsan and local application of stabilarsan to the ulcers.

Case 3.—Female, aged 50. Unmarried. Ill health began with demonstrated duodenal ulcer in 1923. The main events since that time in chronological order were gastro-enterostomy and appendicectomy, continued pain, jejunal ulcer, gastrectomy, continued pain, obstruction of descending colon (believed to be malignant, operation showed it to be spastic), anæmia, achlorhydria, sores in mouth, wasting. Hb less than 40 per cent (1931).

Came under writer's care after interval of seven years. Specific treatment, clinical relief.

Relapsed after three months—cycle of nursing home, consultations, etc., repeated. Further operation for supposed carcinoma of colon refused.

Returned to writer—ulcers of mouth widespread and extremely painful, signs of myocardial degeneration with dyspnœa and œdema of ankles. Three months' treatment, clinical relief.

Early in 1934 developed Argyll-Robertson pupils and delusional insanity, and has since been in a mental home with a confirmed diagnosis of cerebral syphilis.

Prior to Christmas, 1933—that is, for ten years—the writer's diagnosis of syphilis was rejected by many consultants representing several London teaching hospitals, on the ground of a negative Wassermann reaction. This diagnosis was finally confirmed by the late Dr. James Collier on the basis of insanity, Argyll-Robertson pupils, and the tongue, which by this time had become typically fibrotic.

For the present purpose it suffices to mention the persistent painful superficial ulcers of the mouth, which were relieved by intravenous arsenic and by no other remedy.

Summary and Conclusions.—Three examples of a rare form of stomatitis are described, the feature being pain and chronicity in large recurring superficial ulcers of the buccal and pharyngeal mucous membrane. The Wassermann reaction was negative in all three, but evidence of syphilis is conclusive in one, good in one, and absent in the third (except the suggestive enlarged epitrochlear glands). Both the syphilitics were congenital.

Intravenous arsenic—with intramuscular bismuth added as a precaution—cured all three cases.

An unusual number of consultants had seen two of the patients, but the syphilitic nature had not been recognized, and treatment on other lines had been without effect.

CHAPTER XV

PES CAVUS AS A PHYSICAL SIGN IN CLINICAL MEDICINE

A REFERENCE to the literature on claw-foot will show that the deformity is universally approached from the orthopædic side. The student is taught, and may continue to believe, that if treatment is required at all it will consist either of correcting boots, manipulation, or operation.

Pes cavus is classified as congenital and acquired, and various causes are known. Congenital cases may be associated with spina bifida, or may not become evident till the sixth or seventh year or later. Acquired cases may develop from a transient paralysis of the extensor muscles in poliomyelitis or in such diseases as Friedreich's ataxia. The deformity is such as would be expected from a temporary weakness or paralysis of the sole muscles supplied by the external plantar nerve, and is therefore comparable with ulnar paralysis in the hand. Evidence is strong that the primary disease is in the central nervous system. In no orthopædic text-book available to the writer is it suggested that treatment should be directed to the underlying nerve disorder. During 15 years' practice he has not seen a case of pes cavus requiring surgical treatment, and only one each

secondary to poliomyelitis and Friedreich's ataxia. There have, however, occurred many instances of moderate pes cavus developing slowly in middle life and discoverable only on general examination, and it would therefore seem that the condition of pes cavus has a significance for the general practitioner very different from that which it has for the orthopædic surgeon. In other words, it is not so much a deformity as a muscle paralysis betraying an underlying nerve disease. An example will illustrate this.

A woman of 62 (*Case* 5) complains of precordial pain, with B.P. 240/120. General examination reveals pes cavus and a perforated nasal septum. The Wassermann reaction is negative, but what disease except syphilis could cause: (1) A cardiovascular lesion; (2) An organic nerve lesion revealed in atrophy of the intrinsic muscles of the foot; (3) Perforation of the nasal septum? Specific treatment was followed by the relief mentioned in the case notes.

Of the six examples to be mentioned, two were congenital and four acquired. In none was there any complaint about the deformity *per se*. The leading symptoms were respectively:—

1. Feet "go on fire" during walking and compel rest.

2. Breathlessness and palpitation in attacks lasting up to one hour.

3. Pain in legs.

4. (*a*) Fits of shivering associated with desire to defæcate; (*b*) Epigastric pain; (*c*) Spasmodic suboccipital pain.

5. Precordial pain.
6. Long-continued cough.

None of these symptoms suggested syphilis, but a general examination revealed pes cavus in all—in other words, an organic nerve lesion. Other signs, and, in some cases, family history, strengthened the suspicion of syphilis, and treatment of this disease was followed by relief of the leading symptom.

Briefly, the components leading to the diagnosis in the respective cases were as follows :—

In *Case* 1 : (*a*) Feet blue and cold, right knee-jerk absent—i.e., a cardiovascular disorder as well as an organic nerve lesion. (*b*) Tongue (*see Fig.* 19) shows loss of epithelium, mosaic type, milky film on surface. (*c*) Wife has leukoplakia of the tongue, etc. Diagnosis confirmed in the husband by a positive Wassermann reaction.

In *Case* 2 : (*a*) Tongue small with rectangular markings—i.e., evidence of interstitial glossitis. (*b*) Unequal reacting pupils. (*c*) Hands and feet cold and red. This, taken with (*b*), shows disturbance of sympathetic system possibly by a paravertebral lymph-adenitis. (*d*) Father died of locomotor ataxia ; mother has anæmia, dysphagia, and smooth sides to her tongue. Evidence is practical enough to accept congenital syphilis as a basis for treatment.

In *Case* 3 : (*a*) Feet blue and congested—a vaso-motor disturbance. (*b*) Tongue smooth and milky. (*c*) Wife—two out of three pregnancies miscarried ; seven years' dysphagia terminating in carcinoma of œsophagus.

In *Case* 4 : (*a*) General adenitis, including epitrochlears and groups in posterior triangles of neck. (*b*) Father has loss of all deep reflexes. Mother has chronic basal congestion with hæmoptysis, not tuberculous. (*c*) Brother rejected from police force because of erythema induratum of many years' standing. Three months' specific treatment was followed by admission to police force.

In *Case* 5 : (*a*) Precordial pain with booming aortic second sound and B.P. 240/120. (*b*) Perforated nasal septum.

In *Case* 6 : (*a*) ' Fits ' commencing in late middle life. (*b*) Extensor plantar response. (*c*) Only daughter has scars in the neck, anæmia, and spoon-shaped nails with transverse ridges.

The chronic stage of syphilis—that between the end of the secondary stage and the onset of aneurysm or locomotor ataxia—is one that can be studied only by the general practitioner—he only has the opportunity for continuous observation. He can check the progress of the disease by a succession of short courses of treatment whenever minor signs develop ; but if he waits until pathognomonic signs are found, cure is impossible.

Among the minor disorders which call for the deliberate exclusion of syphilis is the nerve lesion which produces pes cavus by paralysing or weakening the intrinsic muscles of the foot. In this class of case the Wassermann reaction is misleading. Pes cavus is named as a sign of congenital syphilis by Menninger and also by Goff.

Case 1.—Male, 73, retired. Complains that his feet "go on fire" when he walks, and he is compelled to stop.

ON EXAMINATION.—Feet blue and cold. Pes cavus (*Fig.* 18). Tongue (*Fig.* 19) shows loss of epithelium, surface a 'milky film'. Right knee-jerk absent. W.R. +. No other physical sign. Feet relieved by course of mercury and iodides, and two years later he reports that he has no difficulty in walking.

Patient is convinced that the curling up of the toes has only come on during very recent years.

Wife: Has had asthma, myocarditis, and a lump in the stomach, which have all been successfully treated with mercury and iodides. She has leucoplakia of the tongue and an adenoma of the thyroid.

Case 2.—Male, 39, clerk. Complains of breathlessness and palpitation daily each morning about 11 a.m. in attacks lasting up to one hour. The heart beats heavily at first and then flutters. Duration, fourteen months.

ON EXAMINATION.—Thin, flat-chested type. Tongue smaller than normal, with rectangular central markings. Right pupil larger than left, both react. Deep reflexes brisk, right plantar response is extensor. No physical signs of cardiovascular disease. Hands are cold and red—patient says they are always like this. Feet cold and red, pes cavus on right side, also a minor degree on the left.

FAMILY HISTORY.—Father died of locomotor ataxia. Mother is anæmic, has smooth sides to her tongue, and has not been able to swallow solids for thirty years.

Case 3.—Male, 60, labourer. Unable to work for four years because of pain in the legs. Bilateral pes cavus, legs and feet blue and congested. W.R. negative in serum and C.S.F. Tongue smooth and milky. No other signs of syphilis.

Wife: Had two miscarriages and one healthy child. She died of carcinoma of œsophagus after seven years' dysphagia.

This man was restored to lasting working capacity by mercury and iodides.

Case 4.—Male, 24, fitter, formerly seaman. History of malaria. Complains of: (1) Each winter he has fits of shivering associated with desire to defæcate; attacks may prevent him working for a week. (2) Pain in epigastrium, worse after food, relieved by vomiting; this pain does not occur at night, but he may wake with a cramp in the stomach. (3) Spasmodic suboccipital pain, and formication over right scapula.

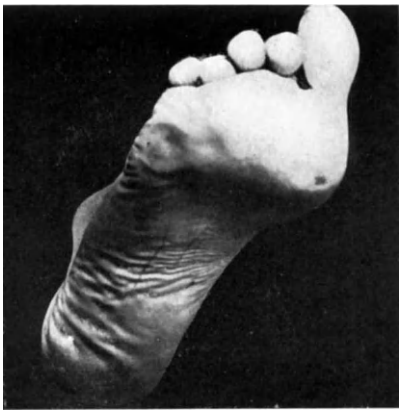

FIG. 18.—*Case* 1. Pes cavus.

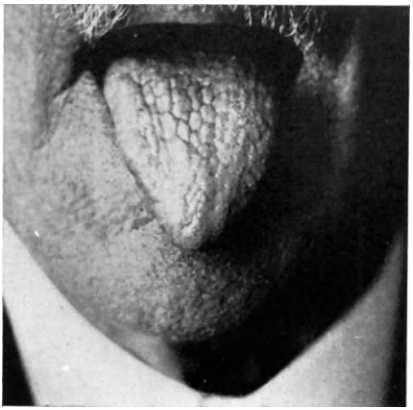

FIG. 19.—*Case* 1. The tongue.

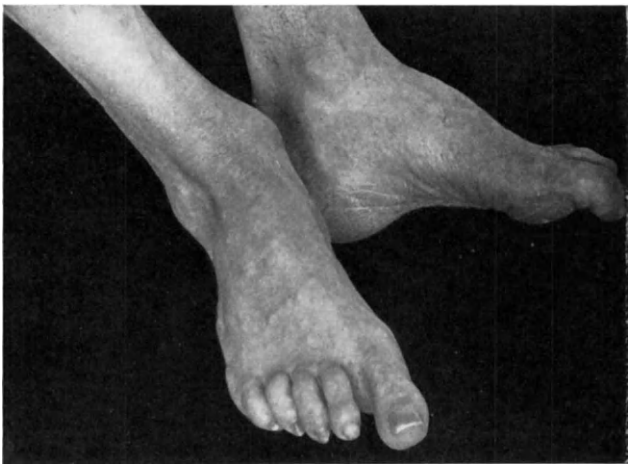

Fig. 20.—Another case of pes cavus. W.R. +.

Fig. 21.—The finger-nails in the same case.

ON EXAMINATION.—Habit spasm of face. Reflexes brisk. General adenitis, including epitrochlears and in posterior triangles of neck. Early pes cavus with hammer-toes and callosities on balls of feet. Serum W.R. negative. C.S.F., 0·425/1000 protein, 10 lymphocytes, slight decrease of glucose, W.R. negative.

Definite relief by antispecific treatment.

Father: All deep reflexes absent, cured of abdominal pain and vomiting by mercury and iodides. W.R. negative. *Mother*: Chronic basal congestion of lungs with hæmoptysis, not phthisis. W.R. negative.

Case 5.—Female, 64, widow.

1927.—Precordial pain. B.P. 240/120. Booming aortic second sound. Perforated nasal septum. Pes cavus. W.R. negative. X rays showed no aneurysm and no widening of aorta.

1928.—Cardiac dilatation with congestive failure. B.P. 110/70. Recovered on mercury and iodides and bismuth injections, and B.P. became steady, 170/80.

1932.—Crippling polyarthritis. Bed six months. Complete recovery under mercury and iodides, and well and active in October, 1936.

Case 6.—Female, 69, widow. Complained of long-continued cough. Basal congestion. B.P. 115/80. Pulse 90, regular force and rhythm, no enlargement. Pes cavus with extensor plantar response on right. Is certain that the pes cavus developed fifteen years ago. Subject to ' attacks ', in which she falls to the floor semi-conscious—pulse then rapid and low tension. Complete recovery in twenty-four hours. Has had two attacks of apparently complete right-sided paraplegia with aphasia from which she has made full recovery in one week. Always does well on mercury and iodides. No sign of syphilis except pes cavus and extensor plantar response.

Only daughter has scars on neck, anæmia, spoon-shaped nails with transverse ridges.

Another example of pes cavus is shown in *Fig.* 20; *Fig.* 21 shows the finger-nails in the same patient.

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APPENDIX A

CASES OF CANCER WITH FEATURES SUGGESTING ASSOCIATED SYPHILIS (APPROXIMATELY ONE-HALF OF TOTAL NUMBER OF CANCER CASES)

1	F.	Cancer of liver	Progressive lens change, arthritic knees. No children. W.R. +.
2	F.	Carcinoma of liver	Cerebral degeneration. Husband died of ' softening of brain '. No children. W.R. +.
3	F.	Carcinoma of liver	Many miscarriages. Corneal nebulæ. Husband has angina and W.R. +.
4	F.	Cancer of breast	Completely bald, unequal pupils, rectangular fissures tongue. W.R., 1 M.H.D.
5	F.	Cancer of breast	Unequal pupils, anæmic. No children. Father is luetic.
6	F.	Cancer of breast	Middle-ear deafness. Cardiac arrhythmia, anginal pains, relieved by iodides. Daughter of 7.
7	F.	Cancer of uterus	Nerve deafness. Angina pectoris.
8	F.	Cancer of breast	General chronic exudative diathesis. Low pyrexia for years. Several miscarriages. Husband dropped dead in the street. C.S.F. 0·6/1000 globulin. Otherwise normal.
9	F.	Cancer of breast	Bilateral optic atrophy. Chronic rheumatoid arthritis.

10	F.	Cancer of stomach	-	Unequal pupils, nebulæ both corneæ. Two brothers and sister's husband died of cancer of stomach.
11	M.	Cancer of stomach	-	Wife has abdominal psoriasis and W.R. +.
12	F.	Cancer of stomach	-	Husband's brother has W.R. + +, and states that both brothers contracted a skin disease from a farm servant in youth. No children.
13	F.	Carcinoma of stomach	-	Husband has chronic arrhythmia; he is one of four brothers, healthy except that one has chronic headache, finally relieved by bismuth, mercury, and iodides. Wife of one found dead in bed. Wife of another had cancer of breast and uterus. Wife of third healthy. No children of any of these marriages.
14	F.	Cancer of stomach	-	Husband a chronic arteriosclerotic, died of carcinoma of liver. No children.
15	F.	Cancer of rectum	-	Three miscarriages. Mother died of a series of strokes. Father has bilateral chronic glaucoma with iridocyclitis. Son has depressed bridge of nose, high forehead, and W.R., 1 M.H.D. Son's C.S.F. 1/1000 globulin, 5 lymphocytes, other characters normal.
16	F.	Cancer of rectum	-	Brother has stigmata of congenital lues.
17	F.	Cancer of rectum	-	Simple ovarian cyst removed five years before cancer developed. No children.

18	F.	Cancer of rectum	-	Myxœdema, cardiac arrhythmia. Unequal pupils. Simple ovarian cyst removed 1925. Cancer of rectum, 1931. W.R. negative. C.S.F. 0·3/1000 protein, 2 lymphocytes per c.mm., glucose decreased. W.R., 1 M.H.D.
19	F.	Cancer of uterus	-	Chronic cardiorenal, with retinal hæmorrhages and with auricular fibrillation. Chronic arthritis. Responds to iodide. Only child has primary glaucoma and an adenoma of thyroid.
20	M.	Cancer of œsophagus	-	No children. Wife is scraggy anæmic type; in her family are several luetics.
21	M.	Cancer of œsophagus	-	Long-standing facial palsy. Thin and wizened for years. Died at 45. W.R. negative.
22	F.	Carcinoma of œsophagus		1920: Palpitation, anæmia, dyspnœa. 1924: Glands, neck and nasal popypi. 1926: Widespread urticaria. 1928: Carcinoma of œsophagus.
23	M.	Intrathoracic growth	-	1926: Sciatica for several months. W.R., 1 M.H.D. 1929: Aphonia and widespread congestion of bases of lungs, improved on iodide for six months, till signs of tumour developed. Sister has palpitation and anæmia. Pupils unequal. Nebulæ both corneæ attributed to inflammation of eyes at 15, which lasted 3 years.

24	F.	Carcinoma of peritoneum	Primary focus not recognizable at operation. No children. Husband has chronic granular pharyngitis. Chronic acne of forehead. W.R. ±.
25	F.	Carcinoma of peritoneum	Attacks of palpitation and dyspnœa with albuminuria 5 and 10 years respectively before death. Thyroid adenoma with toxic symptoms. Finally general carcinomatosis of peritoneal cavity; primary focus not recognized.

APPENDIX B

Some Histological Findings in Latent Syphilis and Cancer

The process of making post-mortem examinations and procuring microphotographs of sections is too time-consuming and expensive for regular adoption in general practice. As mentioned in the text, I did, however, pursue this course for one year.

Many of the sections, including those shown here, revealed localized infiltration of lymphocytes resembling those which Warthin regarded as pathognomonic of syphilis.

Such scattered areas of inflammation in syphilitics have long been known to pathologists. They were described by Osler, Andrewes, and Jonathan Hutchinson as occurring in syphilitics but not themselves due to the virus of that disease. The late Professor Donaldson, of Guy's Hospital, and Dr. W. H. Grace, Pathologist to the Royal Infirmary, Chester, very kindly gave their opinion on these sections, and said respectively, " pathological, but I cannot say they are syphilitic," and " pathological and might be syphilitic."

The time has come to correlate these scattered areas of inflammation with the symptoms presented by patients suspected of chronic or inherited syphilis and who are relieved by mercury and iodides.

The investigation of the morbid anatomy is beyond my sphere, but the discovery of these infiltrations about nerve-cells in the stomach wall (*Fig.* 22), and widely spread in the root of the mesentery, pancreas, and liver, makes the treatment of indigestion with mercury and iodides rational and no longer empirical. Furthermore it is my experience that the dysphagia and anæmia syndrome is permanently relieved if treatment with iron is supplemented by specific remedies. In other words, treatment with iron seems to me to be symptomatic, whereas that with specific remedies is radical, and the basis of this belief is the evidence of widespread localized lymphatic infiltrations in many organs, including always the spleen. No comment is necessary on the sections from cases of cancer beyond that made in the text.

Case 1.—Syphilis. *Fig.* 22 shows lymphatic infiltrations about the nerve-cells in the wall of the stomach, as does *Fig.* 23 about those in the wall of the œsophagus (*Case* 2). Note the similarity in histological character. *Case* 1 was a syphilitic in whom there were multiple pathognomonic features. She suffered from indigestion for very many years. Auerbach's plexus in the stomach not only controls motility, but also the quality and character of the gastric secretion. Infiltrations such as the above are responsible for gastric symptoms and are to be treated by specific remedies.

Case 2.—Chronic anæmia and dysphagia which terminated in carcinoma of the œsophagus. Similar localized infiltrations to those in the œsophagus (*Fig.* 23) are shown in the liver and suprarenal gland (*Figs.* 24, 25).

Case 3.—Carcinoma of the liver. No primary growth was found. A–R pupils and other signs of lues. (*Figs.* 26–28.)

Case 4.—Primary carcinoma of stomach. Massive secondary deposits in liver. Wife has unequal pupils, and a smooth scarred tongue; two living children, two miscarriages. (*Figs.* 29–31.)

Case 5.—Carcinoma of breast. ? Intracranial secondary deposit. (*Figs.* 32–35.)

Case 6.—Carcinoma of lung. No clinical evidence of syphilis. (*Figs.* 36–38.)

Case 7.—Carcinoma of rectum. Unequal pupils. W.R. negative. Several tertiary syphilitics among wife's uncles and aunts. No children. (*Figs.* 39–42.)

Case 8.—Carcinoma of œsophagus. W.R. +. (*Figs.* 43, 44.)

Case 9.—Carcinoma of stomach. One brother died of carcinoma of stomach, another of ruptured aortic aneurysm. (*Figs.* 45, 46.)

Case 10.—Anæmia and dysphagia, terminating in carcinoma of œsophagus. Note infiltration of lymphocytes between muscle laminæ in *Fig.* 47.

Case 11.—Carcinoma of breast, 1921. Carcinoma of uterus, 1929. (*Figs.* 48–50.)

PLATES ILLUSTRATING HISTOLOGICAL FINDINGS IN LATENT SYPHILIS AND CANCER

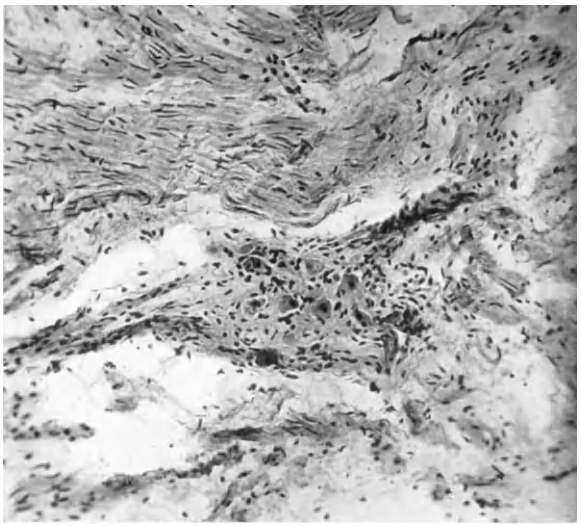

Fig. 22.—*Case* 1. The stomach. (*Low power.*)

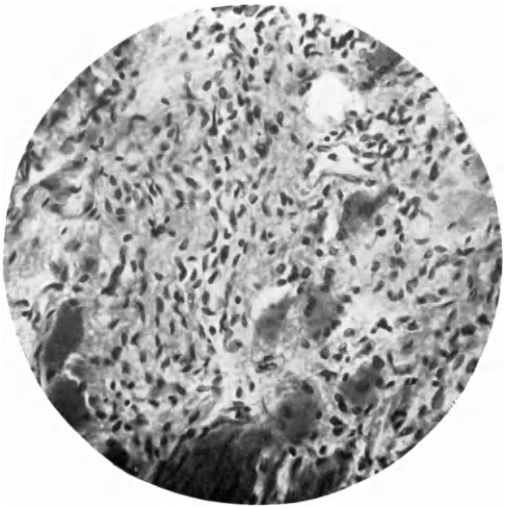

Fig. 23.—*Case* 2. The œsophagus. (*High power.*)

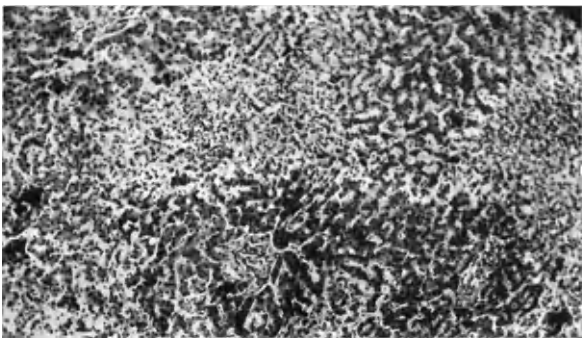

Fig. 24.—*Case* 2 (carcinoma of the œsophagus). The liver.

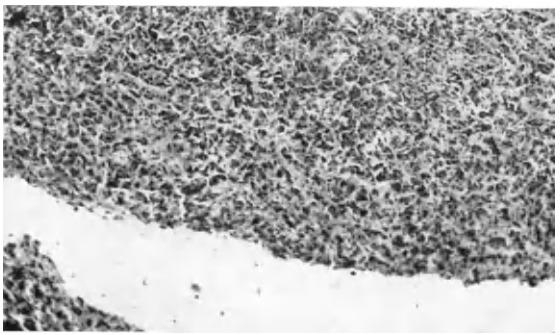

Fig. 25.—*Case* 2 (carcinoma of the œsophagus). The suprarenal.

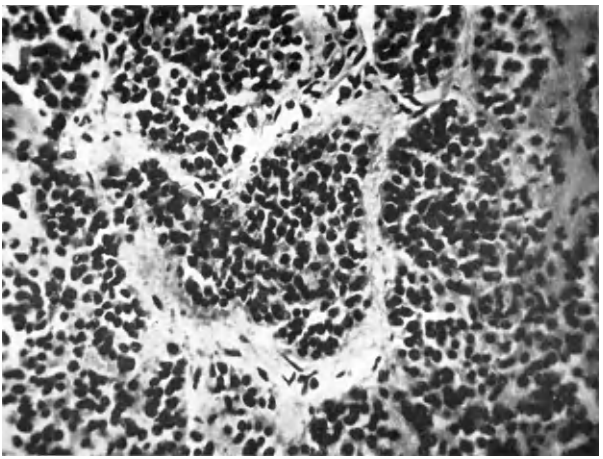

Fig. 26.—*Case* 3. The growth in the liver.

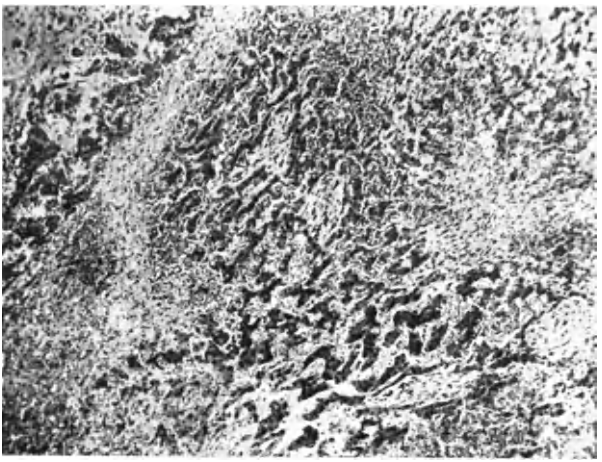

Fig. 27.—*Case* 3. Other parts of the liver.

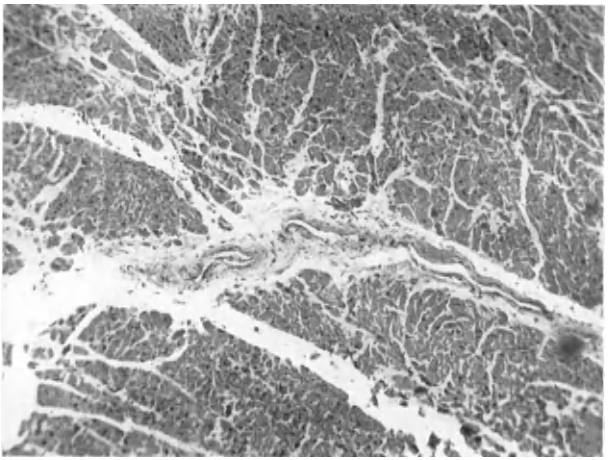

Fig. 28.—*Case* 3 (carcinoma of the liver). The heart muscle.

Fig. 29.—*Case* 4 (carcinoma of the stomach). Part of the liver without growth.

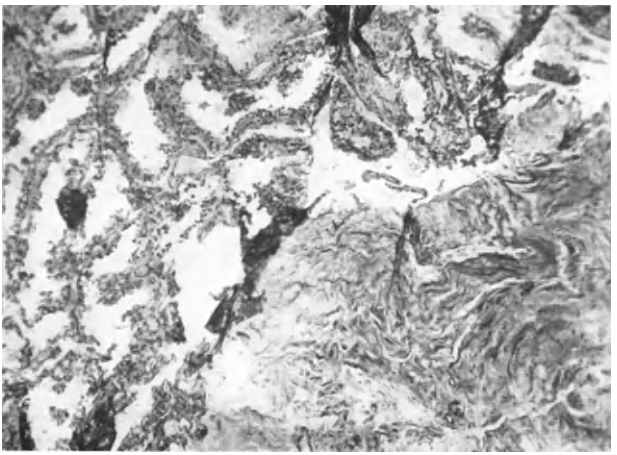

Fig. 30.—*Case* 4 (carcinoma of the stomach). Fibrous nodule in the testis.

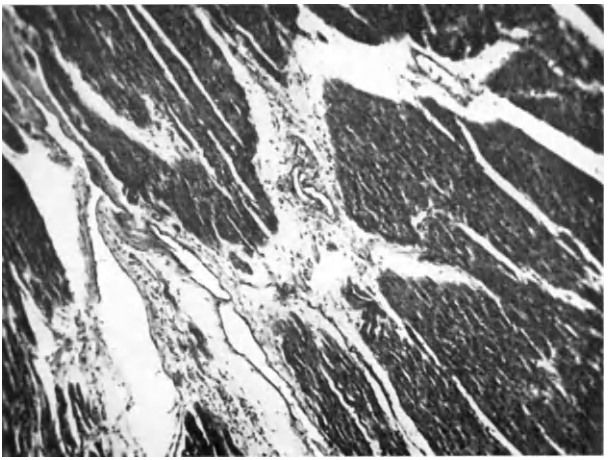

Fig. 31.—*Case* 4 (carcinoma of the stomach). The interventricular septum.

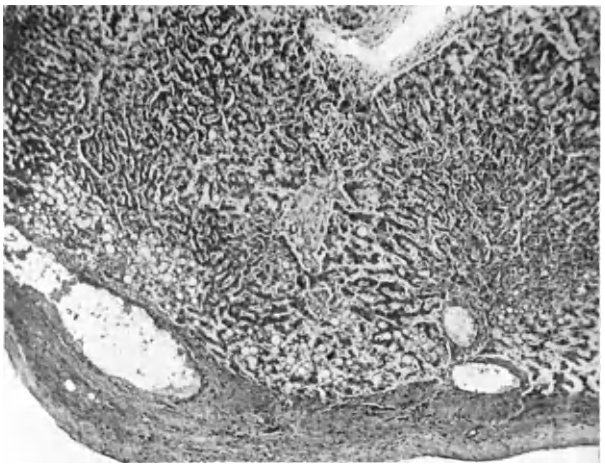

Fig. 32.—*Case* 5 (carcinoma of the breast). The liver.

Fig. 33.—*Case* 5 (carcinoma of the breast). The suprarenal.

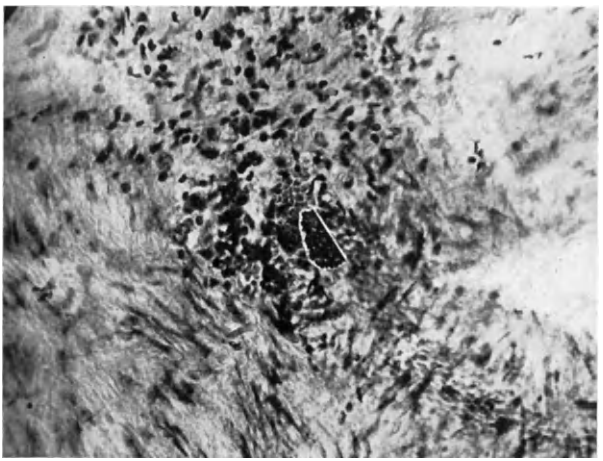

Fig. 34.—*Case* 5 (carcinoma of the breast). Fibrous nodule in suprarenal with perivascular infiltration.

Fig. 35.—*Case* 5 (carcinoma of the breast). The abdominal aorta.

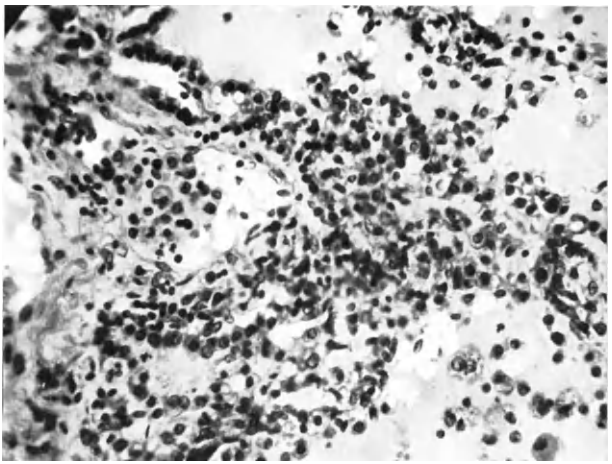

Fig. 36.—*Case* 6. The growth in the lung.

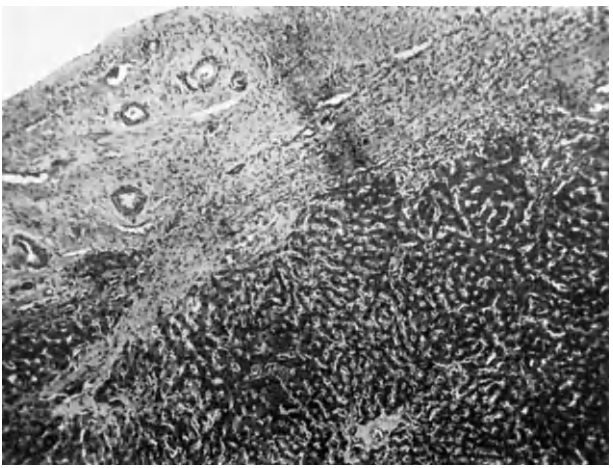

Fig. 37.—*Case* 6 (carcinoma of the lung). The liver.

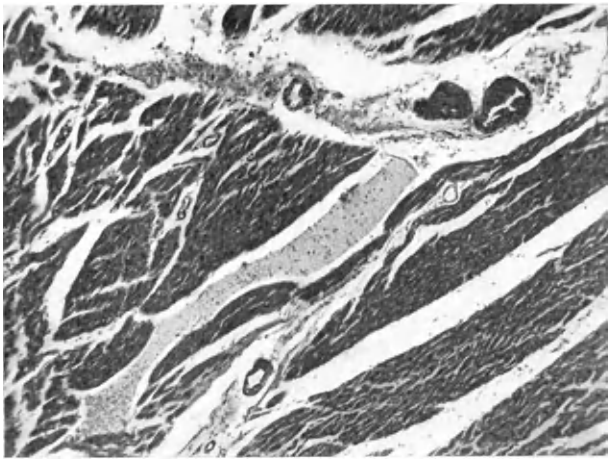

Fig. 38.—*Case* 6 (carcinoma of the lung). The heart muscle.

Fig. 39.—*Case* 7 (carcinoma of the rectum). The kidney.

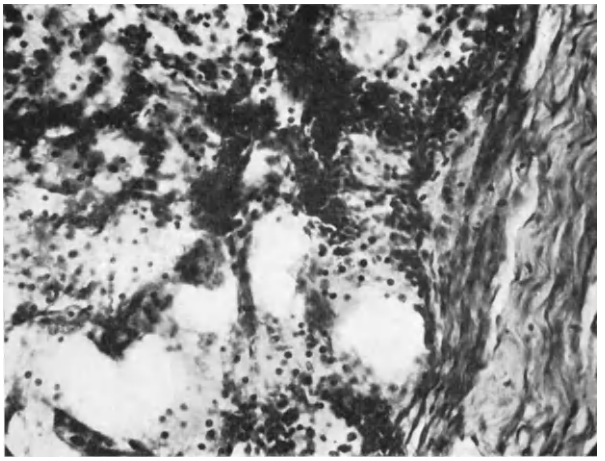

Fig. 40.—*Case* 7 (carcinoma of the rectum). Subcapsular infiltration of kidney. (*High power.*)

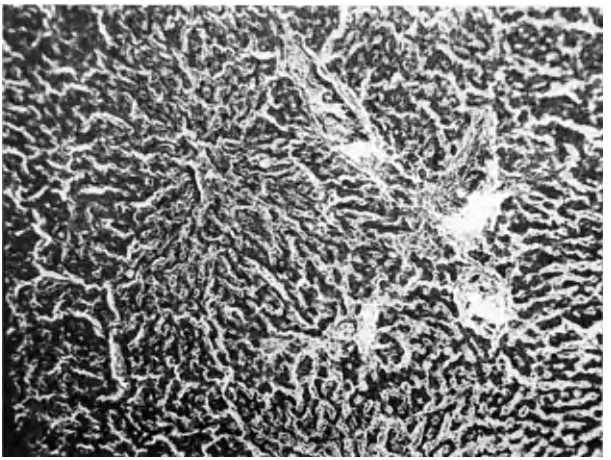

Fig. 41.—*Case* 7 (carcinoma of the rectum). The liver.

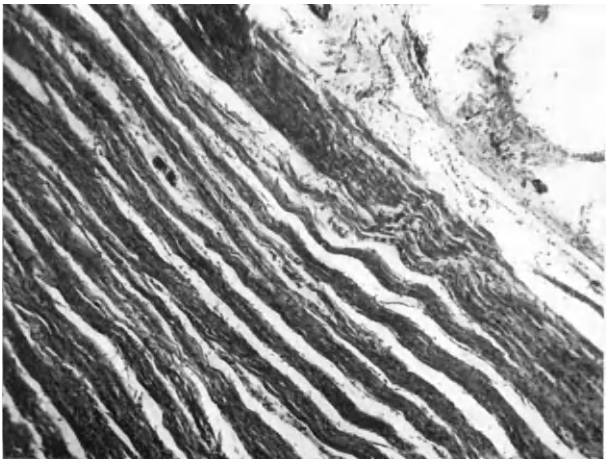

Fig. 42.—*Case* 7 (carcinoma of the rectum). The heart.

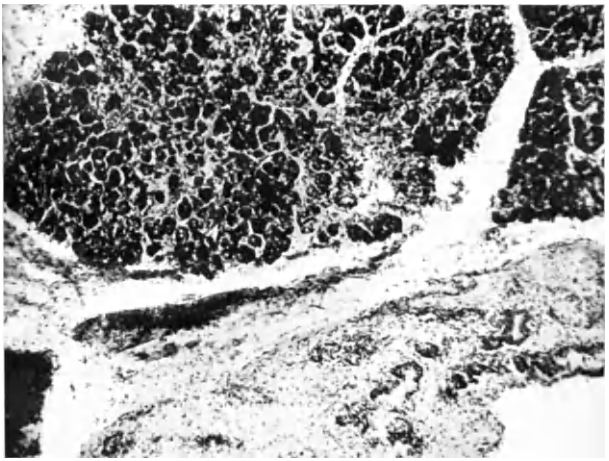

Fig. 43.—*Case* 8 (carcinoma of the œsophagus). The pancreas. W.R. +.

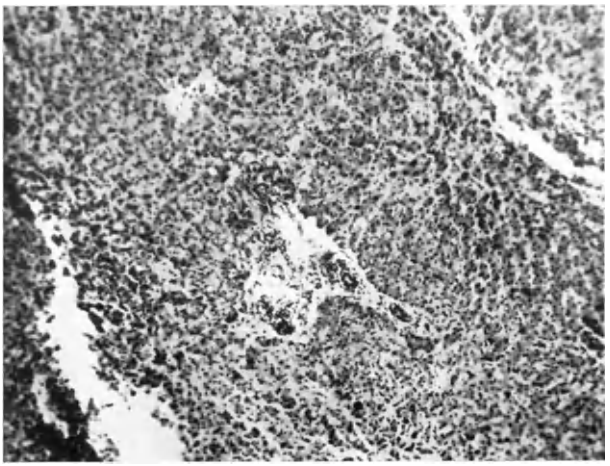

Fig. 44.—*Case* 8 (carcinoma of the œsophagus). The liver. W.R. +.

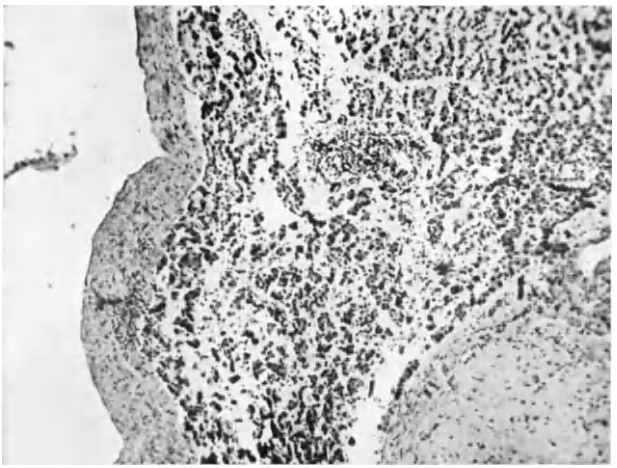

Fig. 45.—*Case* 9 (carcinoma of the stomach). The liver.

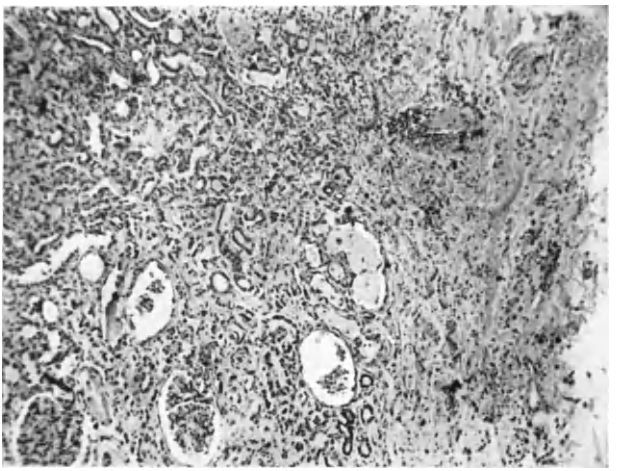

Fig. 46.—*Case* 9 (carcinoma of the stomach). The kidney.

Fig. 47.—*Case* 10 (carcinoma of the œsophagus. The aorta.

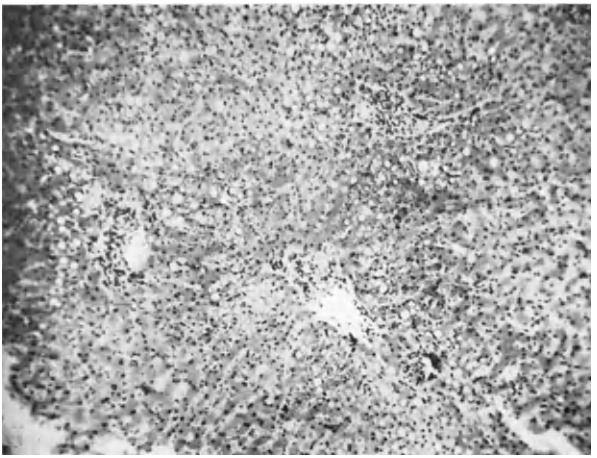

Fig. 48.—*Case* 11 (carcinoma of the breast and uterus). The liver.

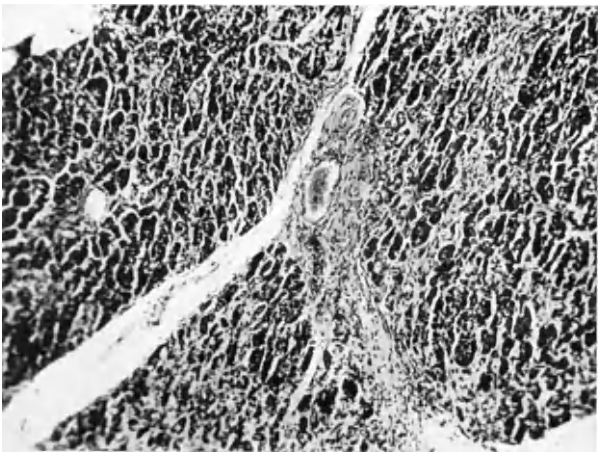

Fig. 49.—*Case* 11 (carcinoma of the breast and uterus). The pancreas.

Fig. 50.—*Case* 11 (carcinoma of the breast and uterus). Vas vasorum in the aorta.