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children 26.3% of glomus tumours were multiple.[5] In adults only two of 685 glomus tumours exhibited infiltrative growth, but seven of the 57 glomus tumours in children showed persistent infiltrative growth.

I have drawn attention to these observations because I am an exponent of the belief that pathological anatomy is not yet a dead subject; there are still many interesting and valuable things to be learned, especially with the aid of tissue culture, the electron microscope and histochemical procedures. If an antiquated fossil such as I can learn new things from this currently despised subject, I hope that there will still be a few pathologists who will find it as absorbingly interesting as it has been to me all of my professional life.

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Chromosomal Abnormalities and Their Relation to Disease

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ABSTRACT

When human chromosome anomalies were first described in 1959, it appeared that specific abnormalities might be correlated with specific syndromes. Mongolism and the D and E syndromes are examples of specific syndromes associated with the presence of an extra autosome. Klinefelter's syndrome may be associated with a variety of different sex chromosome anomalies including XXY, XXYY, XXXY and XXXXY. The last-named variant is the only one that frequently presents features distinguishing it from the others. An XO sex chromosome complex is found in many women with gonadal dysgenesis. However, a variety of mosaicisms have been described in association with this condition, including XO/XX, XO/XXX, XO/XX/XXX, XO/XY and XO/XYY. Extra X chromosomes in phenotypical females do not seem to impair fertility or be consistently associated with congenital anomalies. Two families are described in which chromosome anomalies were found, but the association with defects was irregular. In one family the abnormality involved one of the number 16 chromosomes and in the other it involved one of the small acrocentric chromosomes.

THE advances which led to the detailed study of mammalian chromosomes represented a technical advance in biology.This achievement opened up a completely new field in medicine which has accumulated an extensive literature in only three years. It is not intended in this communication to present a comprehensive review of human cytogenetics but rather to demonstrate examples illustrating the relation between chromosomal findings and the associated clinical and pathological picture.

Several improvements in tissue culture technique were of importance in enabling investigators to study chromosomes in somatic cells. The use of antibiotics and the spreading of chromosomes by hypotonic treatment of dividing cells were perhaps the most important factors contributing to this achievement. Before these recent advances were introduced, human chromosomes had been studied mainly in sectioned material from the seminiferous tubules of the testis. The only surprising fact about the diploid number of 47 and 48 proposed by de Winiwarter[1] and Painter,[2] respectively, is that they were so close to being correct. It was in 1956 that Tjio and Levan,[3] using cultures prepared from lungs of four human fetuses, established the human diploid chromosome number as 46.

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TECHNIQUES

In order to study chromosomes in somatic cells it is not only necessary to induce cell division, but

the number of cells in division must be above a certain minimum level in order to give a reasonable chance of finding cells of high technical quality. To increase the chances of finding cells in metaphase, colchicine is added to the cultures to inhibit spindle formation before harvesting.

Bone marrow cells may be used even without culture,[4-6] though it is usual to examine these after a short period of culture. The bone marrow culture technique as originally described by Ford, Jacobs and Lajtha[7] is relatively straightforward, though results of this procedure are rather uncertain.

The peripheral blood cell culture technique[8] is the method most widely used, but it too presents certain problems, the main one being the variability of mitogenic potency in different batches of phytohemagglutinin. Phytohemagglutinin, which is prepared from navy beans, is essential for cell division to occur in cultures of peripheral blood cells. Various modifications in technique have been proposed, notably one by Hastings *et al.*[9] in which the polymorphonuclear cells are removed by inducing them to ingest iron filings and applying a strong magnet to the culture bottle. Moorhead *et al.*[8] use an air drying technique to spread the chromosomes, but many still prefer gentle squashing for this purpose.[10]

The use of tissue culture in selected cases is a great advantage but is more time-consuming than the blood culture technique. Various tissues may be used, and it is usually the fibroblasts which proliferate at an adequate rate to provide chromosomes for study. At autopsy or operation fascia lata is the preferred tissue as it is easily obtained under sterile conditions and easily cultured. Fibroblasts will grow from fascia taken at varying periods after death, and generally the younger the patient and prompter the refrigeration, the longer the time after death at which successful culture is possible. There are two main variations in tissue culture technique, one in which cells from the primary explant are trypsinized and subcultured,[11] and the other in which cells of the primary outgrowth are studied directly.[12]

SEX CHROMOSOME ANOMALIES

Shortly after the publication of the normal human karyotype,[7] abnormalities began to be described. The first of these were found in Klinefelter's syndrome, Turner's syndrome and mongolism. Since that time, about 50 different chromosome anomalies have been described, many of these involving the sex chromosomes. At first it appeared that specific chromosome abnormalities might be correlated with specific syndromes. To what extent has this proved to be true?

The first human chromosome abnormality was described in a case of Klinefelter's syndrome.[13] The features of this syndrome include small testes, azoospermia, gynecomastia, eunuchoidism, mental retardation and increased production of follicle-stimulating hormone by the pituitary gland. However, testicular atrophy (with resultant azoospermia) is the only constant feature of the syndrome and this only develops at puberty. The testes in prepuberal Klinefelter's syndrome are normal except perhaps for a scarcity of germ cells.[14] The age at which degenerative changes commence in the testis is uncertain but peritubular fibrosis may appear as early as seven years.[15] The atrophy usually progresses until all the seminiferous tubules are replaced by hyaline fibrous tissue, though an occasional tubule with complete spermatogenesis may be seen.

The commonest chromosome abnormality in Klinefelter's syndrome is the presence of 47 chromosomes including an XXY sex chromosome complex.[16] Occasionally some of the body cells may contain normal female (44 + XX) or normal male (44 + XY) chromosomes. This type of chromosome mosaicism has recently been reviewed.[17]

Various other chromosomal variants of Klinefelter's syndrome have been described, including XXYY,[18-21] XXXY[22, 23] and XXXXY[24-29] sex chromosome complexes. The XXYY and XXXY variants do not differ clinically from the commoner XXY type. However, the XXXXY variant of Klinefelter's syndrome may present skeletal anomalies, especially radioulnar synostosis, undescended testes or hypoplasia of the genitalia, and the degree of mental retardation tends to be severe.

The relation between these chromosomal abnormalities and the features of Klinefelter's syndrome is not clear. Testicular atrophy is the only constant feature and yet the presence of at least some chromosomally abnormal cells in the testis does not invariably lead to atrophy.[30]

The relation between mental retardation and Klinefelter's syndrome is even more difficult to assess. Raboch and Sipova,[31] in a study of 47 patients, found that "subnormal values of Raven's test (below 80) existed in practically one in four (12 out of 47)". The incidence of chromatin-positive buccal smears among newborn males was found to be between 0.2% and 0.3%[32-34] while it varied between 0.66% and 1.2% in mentally retarded patients in institutions.[15, 35-38] The number of the newborn males with chromatin-positive nuclei who will later present some mental retardation is unknown.

It would appear from the literature that the XXYY, XXXY and XXXXY variants of Klinefelter's syndrome are always associated with mental retardation, but as these cases have been picked up during buccal smear surveys of mentally retarded patients, this impression is obviously biased.

We may consider sex chromosome anomalies in phenotypical females from the same point of view. The first sex chromosome abnormality to be described in a phenotypical female was in a case of Turner's syndrome.[39] The finding of only 45 chromosomes with an XO sex chromosome complex has been confirmed repeatedly. Many patients with this sex chromosome com-

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plex present with shortness of stature; older patients, primary amenorrhea, but without other stigmata described by Turner.[40] Several other chromosomal variants have been described in gonadal dysgenesis, including various types of chromosome mosaicism. The literature on this subject has recently been reviewed by De La Chapelle.[41]

It appears that in the human the presence of a single X chromosome is rarely associated with the development of normal ovaries. Only a single case has been described in which an XO individual had a child.[42]

The reason for the presence of neck webbing, skeletal anomalies, coarctation of the aorta and genitourinary abnormalities in many patients with an XO sex chromosome complex is not easily explained. Coarctation of the aorta and horseshoe kidneys, both common in chromatin-negative females, are commoner in normal males than in normal females. If this fact were used to argue that the hemizygous X (the presence of only a single X as in normal males and XO females) carries genes responsible for the abnormalities, the analogy could not be extended to neck webbing which is very rare in males.

If a single X chromosome in a phenotypical female is frequently associated with multiple anomalies, what is the effect of extra X chromosomes?

A number of patients have now been described in whom three X chromosomes were found in females with duplicated sex chromatin. The 18 cases described up to the time were reviewed by Johnston *et al.*,[43] and we have data on six other patients with this finding. In addition, the same sex chromosome abnormality has been found in three newborn female infants.[34]

With rare exceptions, the only anomaly described in triple-X females was mental retardation. As most of the cases were discovered during a buccal smear survey of mentally retarded patients, this sample is biased. Indeed, the only common finding in all these patients was the presence of duplicated sex chromatin in interphase nuclei. Most of these patients had normal genital tracts and menstrual history, and two of our patients along with two others discussed in the literature are of known fertility. The 11 offspring from three of these patients had buccal smears, and in every case the findings were normal for the phenotypical sex of the individual. Thus, in none of the 11 known offspring of triple-X females was the extra chromosome transmitted from the mother.

The presence of four X chromosomes has so far been described in only two female patients.[44] As in the case of the triple-X females, mental retardation was the only finding of note, the patients having been found to have three sex chromatin masses in interphase nuclei during a buccal smear survey in an institution for the mentally retarded. As they have been in an institution since childhood their fertility is unknown, but their menstrual history and physical examination of the genital tract were normal.

As in the case of the chromosome anomalies in Klinefelter's syndrome, the relationship between the mental retardation and the chromosome disorder is difficult to assess. It seems likely that some patients with three X chromosomes will be found in the general population.

It appears that extra X chromosomes in the female do not usually interfere with gonadal development and are not associated with a specific syndrome.

AUTOSOMAL ANOMALIES

The commonest chromosome anomaly in man is that described in association with mongolism by Lejeune, Gautier and Turpin[45] and by Jacobs *et al.*[46] This subject alone could form the topic for lengthy discussion and I would make only one comment concerning it. Though mongolism is invariably associated with at least partial trisomy of one of the small acrocentric chromosomes, probably chromosome 21, identical signs are not present in every case. This situation is similar to that found in the D and E syndromes to be described in subsequent paragraphs.

Several patients have been described in the literature in whom an extra small acrocentric chromosome was found but without stigmata of mongolism.[47-52] It is uncertain whether the extra chromosome is number 22, a fragment of some other member in the normal complement or a supernumerary chromosome. These cases form a heterogeneous group and the extra chromosome may not have the same origin in every case.

There are, however, two syndromes in addition to mongolism in which there is autosomal trisomy. The first of these is associated with failure to thrive, flexion and deviation of the fingers, low set and deformed ears, micrognathia, defective ossification and shortness of the sternum, congenital heart malformations and other anomalies. Death almost invariably results in the first few weeks of life. The first example of this syndome was described by Edwards *et al.*[53] Smith *et al.*[54] and Uchida, Bowman and Wang[55] have recently described several such patients. Edwards and his co-workers thought the extra chromosome in their patient was number 17, but Smith *et al.*[54] and Uchida and her coworkers[55] favour the view that this abnormality represents trisomy of chromosome 18. Because of the possible uncertainty, the condition has sometimes been called the E syndrome, after the nomenclature proposed by Patau.[56]

The other autosomal trisomy syndrome was first described by Patau *et al.*[57] It is rarer than the E syndrome, though several cases have now been reported in detail.[58-62] The features of this syndrome include eye defects, polydactyly, apparent deafness, cleft lip and palate, hemangiomata, congenital heart malformations and other anomalies.

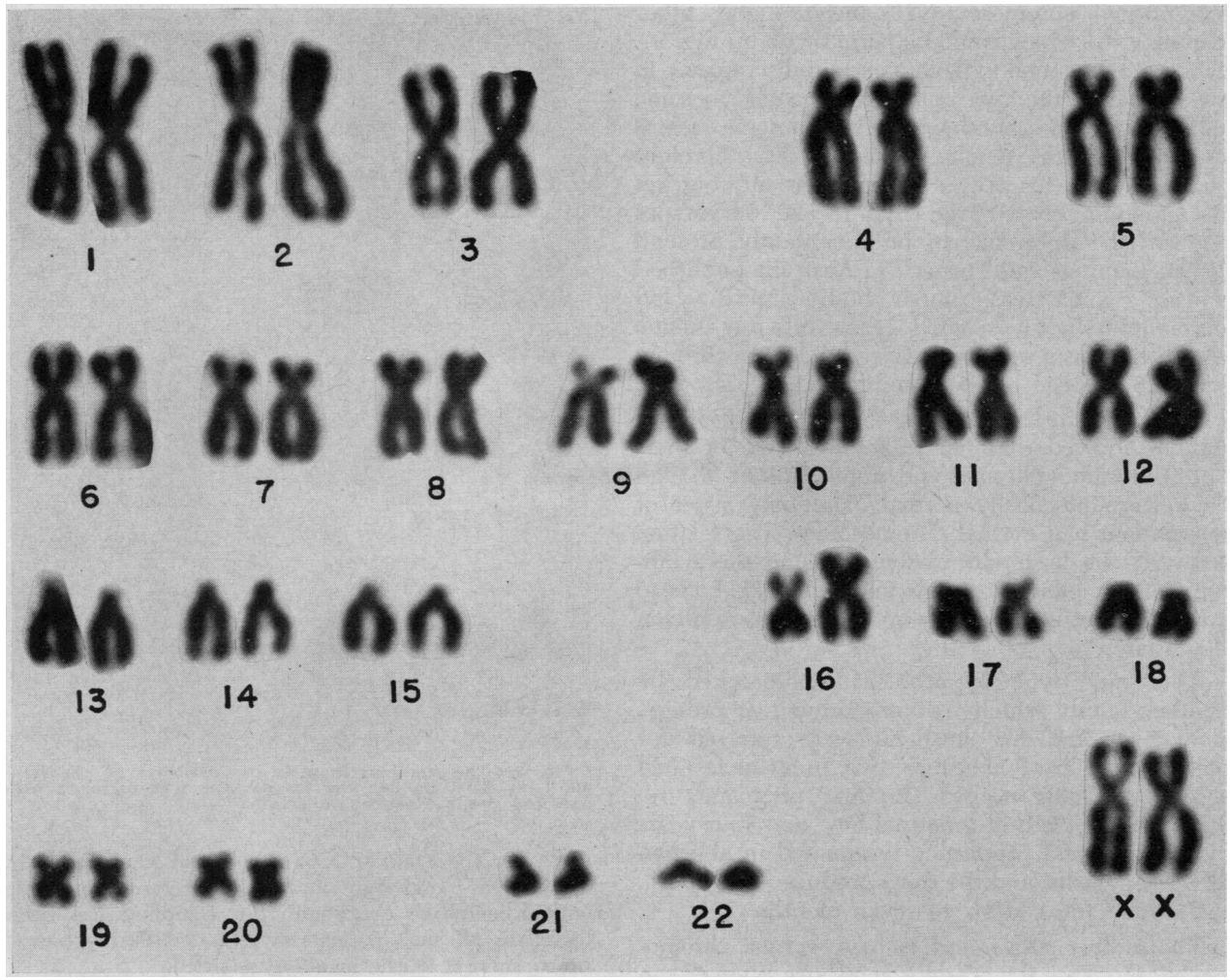

Fig. 1.—Karyotype from patient with several congenital anomalies. The only chromosome which can be paired with the normal chromosome 16 is as long as the shortest members of the 6-12 group.

As in the case of the E syndrome, these defects are usually incompatible with life for more than a few weeks. The extra chromosome in this trisomy syndrome is one of the members of the 13-15 group, and as the members of this group cannot be distinguished from one another, the condition is known as the D syndrome.

All three of these syndromes, mongolism, E syndrome and D syndrome, show a clear-cut relationship between a symptom complex and a chromosome abnormality.

In contrast to these specific clinical syndromes associated with specific chromosome abnormalities, an increasing number of cases appear in the literature in which the relation between symptoms and chromosome abnormality is a matter of conjecture. Some of these problems will perhaps be clarified with the publication of similar cases in the future.

An example of the difficulty experienced in relating symptoms to chromosome abnormalities is illustrated by the cases of ring chromosomes which have been reported.[63-65] These cases do not contribute to the understanding of one another, as a different chromosome was involved in the formation of the ring on each occasion.

Ring chromosomes are formed when there is loss of material from both ends of a rod-shaped chromosome, and it is tempting to assume that this chromosomal loss is responsible for any symptoms which the patient presents. However, it is possible that ring chromosomes could occur asymptomatically in normal people, and in the absence of extensive studies of normal individuals this cannot be ruled out.

An example of the difficulty in relating chromosomal and phenotypical abnormalities is illustrated by the following patient. We studied the chromosomes of a 6-year-old child who presented with torticollis. She had a short broad neck, a small mandible, high arched palate and underdeveloped external genitalia, and was somewhat behind her expected school grade. She was provisionally diagnosed as a case of Turner's syndrome.

Radiographic examination of the neck showed congenital separation of the odontoid process as well as spina bifida occulta of the upper four cervical vertebrae. The buccal smear was chromatin-positive and the chromosome count 46, including an XX sex chromosome complex. There was a considerable discrepancy in size between

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the normal chromosome 16 and the only other chromosome which could be paired with it (Fig. 1). It is quite common to have a certain discrepancy in size between the two members of a chromosome pair,[66] and the number 16 chromosome seems especially prone to show this. It was therefore thought that this was a normal variant, but re-examination of a large number of karyotypes showed the difference to be consistently present. When Jennings and Turner[67] in Australia published a case which was similar both clinically and chromosomally, it seemed reasonable to assume that there was a relation between the large chromosome 16 and the physical findings.

However, further studies on the family of our patient showed that her father and two brothers had the same chromosome abnormalities though they were physically normal. The only sister of our patient had normal chromosomes. The relation between the large chromosome 16 and the symptoms of our patient remains uncertain. We hope to study the family more fully and report the results in detail later.

The same type of problem is illustrated by another family which we are studying at present. A woman and her husband were referred for chromosome study because two pregnancies had resulted in miscarriage. The first pregnancy resulted in the birth of a normal boy, now four years old. The second pregnancy terminated in abortion at three months, and the third produced a stillborn, malformed fetus at six to seven months.

The mother was found to have normal chromosomes but the father's chromosomes showed an unusual anomaly. One of the small acrocentric chromosomes had an extra segment in the short arm (Fig. 2). This appeared to be an insertion rather than a translocation because the satellite was visible on the end of this extra segment. To our surprise the abnormal chromosome was present in the father's mother and also in his normal 4-year-old child.

One might be inclined to dismiss this as an interesting but fortuitous finding but for the fact that Schmid[68] has reported almost identical findings in a family in Texas.

As we do not know the chromosome constitution of the products of the aborted pregnancies, it is impossible to know what relation, if any, there is between the father's chromosome abnormalities and the abortions. The study of this family is continuing and will be reported in detail when completed.

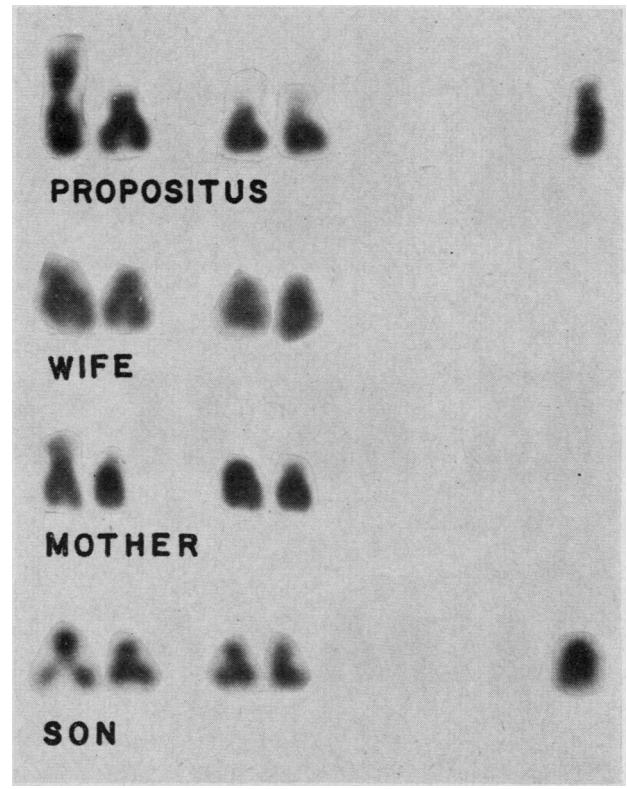

Fig. 2.—The small acrocentric chromosomes of a normal man, his wife, mother and normal son. The patient's wife had had two spontaneous abortions.

SUMMARY

An XXY sex chromosome complex is found in certain phenotypical males whose testes will atrophy at puberty and in whom gynecomastia, eunuchoidism, raised pituitary follicle-stimulating hormone and mental retardation may be found in various combinations designated as Klinefelter's syndrome.

XXYY, XXXY and XXXXY sex chromosome complexes have been found only in mentally retarded patients with Klinefelter's syndrome, but sampling has been biased as all such patients were found during buccal smear surveys of the mentally retarded.

An XO sex chromosome complex is found in many women with gonadal dysgenesis. Infertility is almost invariable, and many such patients also have anomalies involving the skeletal, cardiovascular and genitourinary systems.

Extra X chromosomes in phenotypical females do not seem to impair fertility or be consistently associated with congenital anomalies but are perhaps responsible for a raised incidence of mental retardation among these patients.

Three specific autosomal trisomy syndromes are known in man: mongolism and the D and E syndromes. The chromosomes which are trisomic are a small acrocentric (probably number 21) in mongolism, a large acrocentric in the D syndrome and probably chromosome 18 in the E syndrome.

Other cases have been described in which an extra small acrocentric chromosome was found. These cases do not show any uniform pattern, and the extra chromosome material may not have had the same origin on each occasion.

Ring chromosomes have now been reported in four patients. As the ring does not involve the same chromosome in any two cases, no uniform pattern is expected or has been found.

Two families with different chromosome abnormalities have been briefly discussed to illustrate the frequent difficulties which arise in relating symptoms and signs to chromosomal anomalies.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

THE YOUNG LAENNEC

In 1795, at the early age of fourteen years and seven months, he began the study of medicine and was officially attached to one of the military hospitals as "surgeon of the third class," a position corresponding to that of surgical dresser. The civil war had necessitated the creation of new military hospitals, and the work of the medical school at the Hôtel Dieu (now the Temple of Humanity) had been interrupted, but dissections were continued at the Hôtel Dieu in a room beneath and communicating with one of the wards. Physics and chemistry were taught at the "Ecole centrale."

The devoted uncle watched with pride the growing talents of the young student, though at times distressed by his irrepressible tendency to compose verses and to spend long hours in his natural history studies. In the letters to his father and stepmother a delightful picture is given of the inner life of the lad at this period, with its hopes and disappointments. Money was scarce, the times were perilous; it was difficult to get the necessaries of life, and such luxuries as dancing and flute playing did not appeal to the hard-pressed uncle. The young Laennec found it hard to get anything from his ne'er-do-well father, to whom, after an absence of nine years, he paid a visit at Quimper (1797). The stepmother wished him to take up some business, and it was only a strong appeal on the part of Dr. Laennec that frustrated her designs: "For God's sake let him come back to me as I sent him to you, good, gentle and studious; let him pursue in peace a course of study which is good for his health, sufficient for his fortune and honourable for his reputation,"—and he had his way. The lad walked to and from Quimper to Nantes in four and a half days at the rate of about forty-one kilometres a day. There are sad letters telling of many trials and worries, lack of proper clothing, no money for books, or for his fees, and the uncle too hard-up to do anything, and the father too careless to answer letters. After following for five years the courses at the Hôtel Dieu and the work at the military hospital, Laennec passed the examination for the grade of "Officier de santé."

In 1800 a widespread insurrection occurred in the west, and for a time he served with the regular army in the field. Then followed a period of great anxiety and depression. The desire of his life had been to finish at Paris, but there were no funds, and a sixth year of hope deferred had to be spent at Nantes. At last the fledgling took flight, and in 1801, with a light heart and light pocket, with only eight hundred francs, the young Théophile set out to conquer Paris. In those terrible days Nantes had been a hard school, but he had laid a good foundation in practical work, he had picked up a fair education, and above all he had developed an intense love for his work. He had given play to a poetic temperament and Professor Rouxeau gives a number of small poems, some of which indicate that a certain "Nisa" had stirred his Breton heart. With a group of old Nantes students and friends he was soon at home in Paris, and at once attached himself to the Charité Hospital, where Corvisart had already revolutionized the teaching of medicine.—Sir William Osler: Men and Books, *Canad. Med. Ass. J.*, 3: 138, 1913.