AYERZA'S DISEASE, SILICOSIS, AND PULMONARY BILHARZIASIS

BY

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Ayerza's disease was first fully described in a monograph by Arrillaga, of Buenos Aires, in 1913. Arrillaga claims that it is a morbid entity with a fairly constant clinical course and picture terminating with cardiac failure and an extreme degree of cyanosis, the latter feature leading him to give it the name "cardiacos negros." The subjects are adults. The predominant pathological change is sclerosis of the pulmonary artery and its branches. The lungs also show chronic changes, a fact which brings the entity into the group of cardio-pulmonary diseases. The aetiology and the cause of the extreme cyanosis have been regarded as somewhat of a mystery. Syphilis was formerly thought to be the cause of the pulmonary arteritis, but this has been disproved.

Since the publication of this monograph a number of cases considered to be of a similar nature have been recorded under such titles as Ayerza's disease, pulmonary arteriosclerosis, and sclerosis of the pulmonary vessels. These cases form a motley group. They come from various parts of the world in small numbers, often single examples. The subjects are of all ages, many in very early life. In a few instances the aetiology is obvious—such as those cases with congenital cardiac lesions. An occasional case is claimed to be syphilitic. Many are ascribed to the end-results of chronic lesions of the lung parenchyma, thus belonging to the cardio-pulmonary group. When advanced cor pulmonale has developed and the heart fails there is inevitably cyanosis, but only in a few instances has it approached the extreme degree described by Arrillaga.

This heterogeneous collection of cases of varying aetiology and manifestations clearly cannot explain the frequency and the consistent features of the disease described in Brazil. What, then, is the explanation of its presence in this geographical area?

Pulmonary Bilharziasis

In the course of the last twenty years studies by members of the Faculty of Medicine of Cairo have gradually uncovered manifestations of lesions of the pulmonary artery and its branches produced by the action of bilharzial ova. Modern progress started in 1928 with the description by Sorour (1932) of the pathology, and Azmy and Effat in 1932 gave the first clinical account of two cases diagnosed during life. These pioneer communications were followed by clinical records by Day (1937) and by a very full pathological study by Shaw and Ghareeb (1938).

Since that time progress has been rapid, with studies by Moussa (1942), Bedford *et al.* (1946), Khatlab (1946), Kenawy (1947), Erfan (1948), and others. These communications are of great interest and may be referred to for full details.

The clinical symptoms and physical signs, the radiological appearances of the lung and cardiovascular system, and the course and progress have been pieced together and correlated with the morbid anatomy. It is now possible to diagnose the condition clinically and radiologically at a fairly early stage during life, and numerous cases are being recognized.

Briefly, the initial morbid process may be said to be obliterative endarteritis of the small branches of the pulmonary artery resulting from the action of ova which reach the site as emboli. With repeated reinfections the

process extends centrally. Finally, the main branches of the pulmonary artery may become dilated to aneurysmal proportions and cor pulmonale develops. The lung parenchyma, however, remains uninvolved or only slightly affected, and fibrosis is completely absent. So long, therefore, as the right ventricle, by hypertrophy, is able to force enough blood past the obstruction the lung tissue can oxygenate it satisfactorily. Hence cyanosis does not develop till the heart fails, and even at that stage cyanosis never reaches the degree described in cardiacos negros. The gross changes in the pulmonary artery and its branches led Shaw and Ghareeb to suggest the name of Egyptian Ayerza's disease for advanced cases. This has often been used, but the condition is now more generally known as cardio-pulmonary or pulmonary bilharziasis.

These cases prove that advanced disease of the pulmonary artery and its branches does not of itself produce cyanosis. The cases in Egypt also differ substantially from those in Brazil in the mildness or absence of pulmonary symptoms, though certain allergic manifestations such as asthma are now being studied.

Is Silicosis the Primary Factor?

Thus there are two geographical areas in which sclerosis of the pulmonary artery and branches occurs with considerable frequency but with certain differences in the clinical course. The Egyptian group proves that the special features of Ayerza's disease in Brazil cannot be ascribed solely to the changes in the pulmonary artery and its branches.

The Egyptian delta is a flat country lying little above sea-level and completely devoid of mines, and the subjects of pulmonary bilharziasis are nearly all farmers or from the families of farmers. The Brazilian subjects, on the other hand, are gold-miners working in valleys at an altitude of 14,000 feet (4,270 metres) in the Andes. The occupation suggests that silicosis may be the primary aetiological factor, while the tremendous altitude may account for the unusually high degree of cyanosis. Ayerza's disease thus can be reasonably explained as the result of silicosis occurring at great altitudes.

Dr. K. O. Courtney, of the Canal Zone Medical Service, who is familiar with the locality, states in a verbal communication that the cases with cardiac failure were formerly brought down to the plain by train. The railway rises to 16,000 feet (4,880 metres) before starting the descent, and deaths during the journey were not uncommon. Patients are now brought down by air. It is observed that on reaching the plain the cyanosis improves.

Pulmonary bilharziasis is unlikely to be the principal factor in Brazil in view of the long pulmonary course. *Bilharzia mansoni* is the only type present in Brazil, and ova of this variety cannot reach the lung until after the development of bilharzial cirrhosis of the liver, which is accompanied by splenomegaly, but it is possible that the condition of the liver and spleen respectively might have been erroneously ascribed to alcohol and malaria, both of which are mentioned by Arrillaga as aetiological factors. The existence of pulmonary bilharziasis, so far as I am aware, has not been reported in Brazil, though it must almost certainly occur there, and a case in Porto Rico was reported by Clark and Graeff (1935). The histology of pulmonary bilharziasis is so specific that it can be readily diagnosed when the possibility of its presence is once recognized. The differentiation of silicosis and pulmonary bilharziasis radiologically would certainly present difficulties and has not yet been studied, but there are several parts of the world where the two processes may coexist.

It is therefore suggested that Ayerza's disease as seen in Brazil is the result of silicosis occurring at high altitudes,

while the possibility of pulmonary bilharziasis as a main or contributory factor should also be borne in mind.

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THE INCIDENCE OF CANCER OF THE UTERINE CERVIX

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Although cancer of the uterine cervix when taken early is to a large extent curable, the proportion of cases coming to treatment at an early stage is so small that little impression is being made on its mortality rate. Not one case in ten reaches hospital with the disease confined to the uterus, and many come with such extensive lesions that only palliative treatment is possible. In spite of the efforts expended in educating the public on cancer, and the emphasis placed on the subject in our medical schools, much delay is still due to ignorance and neglect, but late diagnosis is also attributable in large measure to the insidious manner in which the disease develops. In cancer of the cervix there is no close correlation between the length of history and the extent of the disease, and more than half the women seen at Cardiff Royal Infirmary within three months of the first symptom are classified as having a stage 3 or stage 4 cancer (Maliphant, 1947).

Whereas early cervical cancer is usually symptomless, many cases are devoid of symptoms until they are far advanced, and this clinically mute phase is one of the main obstacles to early diagnosis. It is for this reason that in some countries, and notably in the U.S.A., women of cancer age are now being encouraged to undergo periodic gynaecological examination as the best and often the only means of ensuring prompt diagnosis. Cancer detection clinics have been established in most large centres, and the number of cases of cancer discovered in presumably well individuals has been so high that the representative character of the persons attending the clinics has been questioned (Jones and Cameron, 1947).

In the extensive literature on cancer of the cervix very little information is available on the number of living persons afflicted with the disease, and the purpose of this inquiry is to ascertain its incidence rate, together with the relative probabilities of the disease developing in the various age, civil state, and parity groups of the population. Such data would not only provide information on the number of new cases that would be expected in a particular group of women but may also have a practical bearing on problems relating to the aetiology and control of the disease.

Women who develop cancer of the cervix are measurably different from other women, and an attempt is first made to ascertain the degree to which the cancer hazard is affected

by such variants as age, marital status, and parity. Many reports have shown the distribution of such characteristics in women who develop or die of the disease, but they have rarely shown the distribution of the same characteristics in the community from which the cancer patients have been drawn. It is with this object in view that our patients have been examined against the background of the local population. At Cardiff Royal Infirmary 1,200 consecutive cases seen during the 25-year period 1922-46 have been analysed: 80% were residents of Glamorgan. As 1931 was close to the middle year of this observation period the 1931 Census figures were used in the main as the standard of comparison. The age, civil state, and child-bearing experiences of the community are then correlated with the tendency to develop cervical cancer.

Age

In this series 98.5% of the patients were married, and their ages ranged from 20 to 80 years. Their distribution by age is shown in Table I, together with that of married (widowed and divorced) women in Glamorgan at the 1931 Census.

TABLE I.—Distribution by Age

Age Group (Years)	Cancer of Cervix. C.R.I., 1922-46		Married Women of Glamorgan: 1931 Census		Estimated Relative Risk of Contracting the Disease (a) as % of (b) (c)
	No.	% (a)	No.	% (b)	
20-24	5	0.4	15,877	5.2	7
25-29	14	1.2	32,306	10.7	11
30-34	53	4.4	38,399	12.7	35
35-39	123	10.2	38,540	12.7	80
40-44	162	13.5	35,692	11.8	114
45-49	205	17.1	33,164	11.0	155
50-54	211	17.6	30,214	10.0	176
55-59	187	15.6	25,443	8.4	186
60-64	126	10.5	19,798	6.5	161
65-69	75	6.2	14,603	4.8	129
70+	39	3.5	18,509	6.2	56 ?
	1,200	100	302,485	100	

Although cancer of the cervix may be seen at extremes of age, it is predominantly a disease of middle life, and only 20% of the patients had reached the age of 60. A little less than one-third (30%) were under 45, a little over one-third (36%) were 55 or over, and the remaining one-third (34%) were in the decade 45-54 years. It is not so much the age of the individual as the senescence of the uterus which determines the occurrence of the disease, and if regard be paid to the number of women living at a given age it is observed that the cancer hazard continues to rise until the age of 60. The risk in the various age groups may be expressed by showing column (a) of Table I as a percentage of column (b). It is noted that the relative risk of the disease developing increases enormously from age groups 25-29 to 30-34, and at ages 35-39 it is more than twice as high as at ages 30-34. The rate of increased relative risk continues to rise until the peak is reached at ages 55-59. From this point it shows a steady decline, the rate becoming steeper and steeper in older women. Beyond the age of 70 this gradient is probably fictitious, as our series, in common with others compiled from hospital figures, is likely to be deficient in women over this age.

Lane-Clayton (1927) has drawn attention to the divergence between the age incidence of uterine cancer as shown by hospital figures and by mortality rates. The older the individual the less likely is she to attend hospital, but Mackenzie (1939) has shown that it is not until the age of 70 is reached that age as such acts as a serious deterrent to obtaining treatment. The inclusion of missing cases at ages of 70 and over in the above series would mean an adjustment throughout the entire percentage distribution, and