MAN AND HIS CULTIGENS

AN INQUIRY INTO THE ECOLOGY OF CHRONIC DISEASES POSSIBLY AFFECTING 3% OF THE POPULATION

The appreciation of the epoch making ecological changes brought about by the transition from food-gathering to food-production by man associated with the discovery of cultigens — cultivated plants and domesticated animals — is exerting a strong influence on many medical concepts and on research.

Livingstone[1] when discussing the sickle cell gene, Levine[2] infant nutrition, Yudkin[3] coronary disease and Cleave[4] peptic ulceration, have all indicated the crucial importance of food production, processing, and other environment changes as possible factors in the origin of disease.

Hypotheses suggesting that environmental changes (methods of obtaining food which in turn influence dietetic habits) caused by human evolution have led to diseases of maladaptation, are paralleled by concepts which interpret how diseases in turn can alter the course of this evolution.

In the field of rheumatic disorders the currently prevailing theory of autoimmunity has failed to establish causes or promote cures[5]. An alternative concept has been advanced by the present author (1963)[6]. This concept is based on the postulate of man's maladaptation to biologically new food. Evidence for the presence of this maladaptation, considered in this concept to be the genetic (inherited) susceptibility to rheumatic diseases, is based on: (a) clinical observation; (b) a pilot trial of treatment, 1964[6]; and (c) recent advances in biochemistry, genetics and gastroenterology including the study of the small intestine on the one hand and clues from paleopathology on the other. In addition, the widely recognised interpretations of history and of recent archaeological findings in connection with the discovery of cultivation [7,8,9] provide intersecting interests with these medical and biological sciences and point to a metabolic origin of rheumatic diseases.

Briefly, in the concept advanced here, it is suggested that the cereals wheat and rye, the biologically new food (hitherto probably only avian food), were not universally suited to human metabolism because of their protein component, gluten.

Thus, the discovery of agriculture, which in evolutionary terms suddenly altered the dietetic habits of man and led to civilisation, might have found his adaptive response to this change biologically wanting.

This abrupt change has occurred during the "Neolithic Revolution" and, while historically remote, it is biologically recent. One of the postulates advanced by the present author is that some diseases associated with civilisation may be caused by this revolutionary change in the dietetic habits. These habits, predominantly carnivorous during pre-paleolithic hunting and fishing cultures, were changed by agriculture, and later by food processing to increased dependence on cereals rather than animal sources for proteins.

Epidemiology of Obscure Disorders

In meeting the challenge of disorders of obscure or unknown origin, modern medicine entered the useful path of epidemiological studies. These aimed at discovering possible environmental and inherited factors and their relative importance as causes of these disorders. These epidemiological studies embrace population surveys and studies of family and occupational community groups.

The prevalence of many obscure disorders can be established by some or all of the methods employed by epidemiology, and these include the following techniques:

(a) a questionnaire: (b) clinical (including radiological examination in chronic rheumatism) and biochemical examinations of the population samples; and (c) obtaining the rates of prevalance of the disorder under study from official mortality figures.

World-wide epidemiological studies are being conducted on chronic rheumatism,[10] multiple sclerosis[11,12,13] and other disorders.

The purpose of international investigations of these diseases is to discover possible ethnic, racial, geographic (climatic) and genetic factors which could throw light on their pathogenesis (mechanism by which disease is produced by the operation of one or several causal factors).

The importance of these studies in relation to multiple sclerosis (a disease in which degeneration of myelin sheaths of nerve fibres leads to a widespread and unpredictable neurological disorder) will be realised if we recall Lumsden's recent statement: "We know less about it than we know, for instance, about the causation of cancer"[14]. But as a result of early

epidemiological studies we do know that at least in Europe and North America multiple sclerosis is a disease of "higher latitude and temperate and cold regions" (Allison) [15].

A recent textbook on this disease[16] suggested that this peculiar geographic distribution of multiple sclerosis is the sole aetiological (causal) factor known so far in this disease and that any theory of its pathogenesis must account for it.

Attempts at resolving this mystery of geographic distribution in terms of solar radiation[17], isotherms[18], magnetic fields[19] and hence sunspots have proved unrewarding.

Moreover, even the latitude theory has suffered a serious setback through a recent epidemiological study in Japan[11]. It was shown in that study that a wide separation in latitude (ten degrees) between the cities of Sapporo and Kumamoto, each equal in population and with similar medical facilities, made no difference to the incidence of multiple sclerosis which, though negligible in both cities, was almost equal.

Another discrepancy in the latitude theory is provided by Queensland. While it must be admitted that epidemiological studies in Australia are still in their infancy and that the figures of the incidence of multiple sclerosis are far from complete, its relative incidence in different States fails to conform to the latitude theory [40]

An important advance in the epidemiology of multiple sclerosis is provided by the study of its prevalence among different ethnic groups in Israel[13].

In the conclusion of this study a suggestion emerged that a **prevalent environmental factor correlating with latitude may be important in the pathogenesis of multiple sclerosis, and that this factor affected those subjects who were constitutionally predisposed to it.**

A virus has been suggested to be this unknown environmental factor[20]. This report suggested an analogy between poliomyelitis and multiple sclerosis but considered that genetic susceptibility plays no part in the causation of this disease. The possibility of genetic susceptibility is widely recognised by clinicians[16] and epidemiologists[13] and it also derives some support from field studies in genetics[21,22].

It is not intended here to recapitulate old arguments for or against infection in multiple sclerosis. It is sufficient to say that clinical observations and epidemiological findings in Japan[11] and in Israel[13] and the still incomplete data from genetics argue strongly against viral aetiology in multiple sclerosis although they do not entirely disprove it.

From the above it can be seen that an impasse has been reached in epidemiological studies of multiple sclerosis.

Indeed, in the search for possible aetiological factors in the pathogenesis of rheumatoid arthritis by epidemiological means, a similar impasse becomes evident. Referring to the incomplete understanding of the significance of the rheumatoid factor (an abnormal protein of the gamma variety of large molecular size which appears in the serum of the majority of subjects with rheumatoid arthritis and in some normal subjects), Gosling[10] states: "We are trying to find the solution for one equation with the two unknowns which according to mathematics is impossible."

World-wide studies of this serum factor have been recently conducted[23] but similar investigations of rheumatoid arthritis are mainly confined to northern Europe and the United States. As yet the knowledge of its incidence as a global phenomenon is limited. Consequently, in spite of these well-designed and expanding epidemiological studies, no new aetiological factors have yet emerged from them which could throw a new light on rheumatoid arthritis. But these studies confirmed the growing opinion that the rheumatoid factor is not one of these aetiological factors[10]. This opinion is also derived from previous human and animal experiments with the rheumatoid factor[24], experiments which failed to indicate its disease-inducing property, thus depriving the prevailing theory of autoimmunity of one of its main props.

I suggest that the lack of progress in the management of rheumatic diseases, which has kept rheumatology in the realm of palliative medicine almost since the days of Hippocrates, could be overcome on the basis of a wider biological and ecological approach to these diseases. This approach to the outstanding problems of contemporary medicine is gaining wider currency in medical thought and research, and provides the basic postulates for the new concept of the pathogenesis of rheumatic diseases advanced by the present author.

The New Concept

According to this new concept of the pathogenesis of rheumatic diseases, they arise as result of a **primary lesion in the small intestine.** This lesion can be explained on the basis of maladaptation to the biologically new food.

Biologically, man appears to have altered little if at all since he emerged as a distinct species—**homo sapiens** — about 1.000.000 years ago. However, since late palaeolithic times, only about 10.000 years ago, his environment has been subjected to drastic changes. It is a biological axiom that the more rapid the change the **less adequate and complete the adaptation.** When man's biological adaptability is considered, a paradox becomes apparent. His power of adaptation to the external environment seems to be limitless; yet in his internal environment he is restricted to the narrowest biochemical and biophysical margins.

He can inhabit the whole planet, from the tropics to the Arctic, from sea level to the heights of the Himalayas. He adapts to underwater existence, and to supersonic speeds in the upper layers of the atmosphere; and now indeed he has lived in orbit. Man can even at times overcome fatal or near fatal mutation such as galactosaemia[25].

But his enzymes are restricted to specific substrates and are the product of a long process of evolution. He depends for most of his vitamins on other living things, and it is not known whether he is capable of wide enzyme induction.

Epochal changes in man's social development which occurred from late palaeolithic times to immediate prehistory are recognised, but the effect of these changes on his biological adaptation requires study. Crucial among these changes was the discovery of cereals relevant to this article, wheat and rye — which in turn led to settled community life and eventually to civilization[7,9]. All ancient civilisations were based on a cereal economy worked by slave labour.

Pre-palaeolithic man, for countless millenia predominantly carnivorous, suddenly changed his diet and adopted those cereals as his staple food.

Perhaps because man lacked the necessary enzymes, the sudden introduction to his diet of cereals containing proteins alien to his metabolism could be the focal biological change of the environment leading to maladaptation. Thus domestication of wheat and rye, crucial to the development of civilization, may be a cause of this maladaptation, which in turn could be the important environmental factor in the pathogenesis of rheumatoid arthritis and other diseases of obscure aetiology.

While these cereals, wheat and rye (or rather their protein-content gluten) can be toxic to some subjects who suffer from gluten-induced enteropathy* or coeliac disease, other living things or their proteins which can produce end-effects leading to enteropathy, could likewise be important in the pathogenesis of these diseases.

It is suggested here, however, that gluten, being contained in a food staple, could be overwhelmingly important as a biological cause of this maladaptation.

Coeliac disease, an inherited disorder, could have been prevalent and severe in prehistoric times, but since it was fatal (until 1952 when its cause was discovered) before reproductive age, it became rare as it is today (1963)[6]. However it still occurs in 1 out of 3,000 to 4,000 births[26,27] and hence probably transmitted as a recessive trait. If this is so, then heterozygotes for this metabolic fault are not uncommon. Indeed, if we apply the Hardy-Weinberg formula for gene frequencies, then on the basis of the figures of the homozygous (coeliac disease) incidence, heterozygous subjects would comprise 3.2 to 3.5 per cent. of the total population. These figures of the incidence would account well for the prevalence of some disorders of obscure causation among peoples subsisting on wheat, oats and rye staples.

If, as implied here, rheumatoid arthritis and possibly multiple sclerosis represent diseases as seen in specific genotypes from that pool of heterozygotes provided by coeliac disease — its homozygous manifestation—it may be asked what compensation tended to perpetuate this type of heterozygote?

It must be noted that for rheumatoid arthritis and multiple sclerosis no single Mendelian gene substitution has been suggested here as the mode of inheritance. It is implied, however, that the heterozygous state carries with it a predisposition, or enhances the risk of developing these diseases by those possessing this genetic trait.

As the risk faces only 3.2 to 3.5 per cent. of the population, the compensating factors relevant to the survival of this type of heterozygote need not be as overwhelmingly potent as those which are encountered in the preservation of the sickle cell gene in 20 per cent. of the population.

While not pronounced and obvious, these compensating factors exist and I suggest that they are to be found in the cushioning effects of civilization (see diagram).

At the inception of civilization and in prehistory, coeliac disease, which would have the effects of a "lethal mutant" gene, would operate in a vastly increased genetic pool provided by a greater population density in civilization as compared with that in the preceding food-gathering, nomadic cultures. This increase was brought about by the discovery of agriculture which offered a relatively more secure food supply. The military and economic might of agricultural States which followed, exemplified by the development of civilization and the power of these States, provided additional security to the individual and his food supply. A reduced death-rate from violence was brought about in part by the utilitarian considerations of the need for man-power for agriculture, and in part by ethical considerations arising from teachings of organized religion. This led to the sparing of lives of captives.

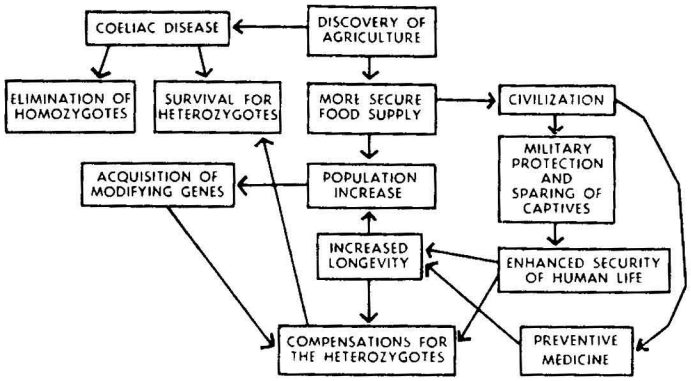
These ameliorative and compensating tendencies leading to an enhanced longevity are continuing today although their forms may be changed. **Preventive medicine** and other positive effects of civilization, in addition to contributing to a longer life expectancy, have also contributed to "releasing latent disease liabilities"[28].

One of these liabilities is rheumatoid arthritis which, unlike coeliac disease, is a disorder as a rule not interfering with the reproductive potentialities of the subject suffering from this rheumatic illness.

When mortality from violence and pandemics ceases to be important in any society, a stage is set for these latent diseases to become clinical syndromes. These conditions exist in most advanced and ethnically European civilizations. It is interesting to note that at least in northern Europe where well-designed and methodologically identical surveys have been conducted, they invariably revealed an analogous incidence of "classical" and "definite" rheumatoid arthritis[29].

These findings, of course, are not coincidental, indeed they probably reflect the operation of similar

COELIAC HETEROZYGOTE AND HIS COMPENSATIONS



Enteropathy is the generic term for lesions of the small intestine.

genetic and environmental factors leading to this disease.

Malaria is not the only selective force operating on mankind. Gluten and coeliac disease are offered here as possible genetic (selective evolutionary) and environmental factors. One would expect that the operation of identical selective forces (coeliac disease) for approximately equivalent numbers of generations (400 since the introduction of cereals*) in a relatively homogenous environment, would yield uniform population gene frequencies (homozygous and heterozygous) in all countries of northern Europe.

I have suggested that the heterozygotes for the metabolic fault (gluten-intolerance) could develop rheumatoid arthritis but only a proportion of them do so. An "out-breeding" in civilization in contrast to "in-breeding" in small nomadic groups would tend to improve the heterozygote's total genetic endowment, possibly through the acquisition of modifying genes (modifiers), thus in part compensating for his partial metabolic disability. This is in accord with R. A. Fisher's theory of "Evolution of Dominance"[30]. One effect, for instance, of these modifying genetic factors could be the acquisition of an intestine which, while not metabolising gluten normally, compensates for it by an improved concentration gradient physiologically or by a greater number of villi per unit area anatomically, etc.

It may be that not only the "expressivity" of the metabolic fault in the totality of genetic endowment determines which heterozygote will develop rheumatoid arthritis.

The "penetrance" of the metabolic fault which is determined by specific environmental modifications could also be relevant in this context.

It may be that only those of the heterozygotes who have a full "penetrance" of this fault will suffer from rheumatoid arthritis.

This penetrance could be modified by environmental factors influencing the dietetic habits. These in turn may vary for the following reasons: personal — related to palatability; (b) social — related to economic status; and (c) regional — leading to some modifications in the diet. This variability in the dietetic habits could alter the ratio of protein intake from cereals as compared with that derived from animal sources.

GEOGRAPHY OF CEREALS & M.S.

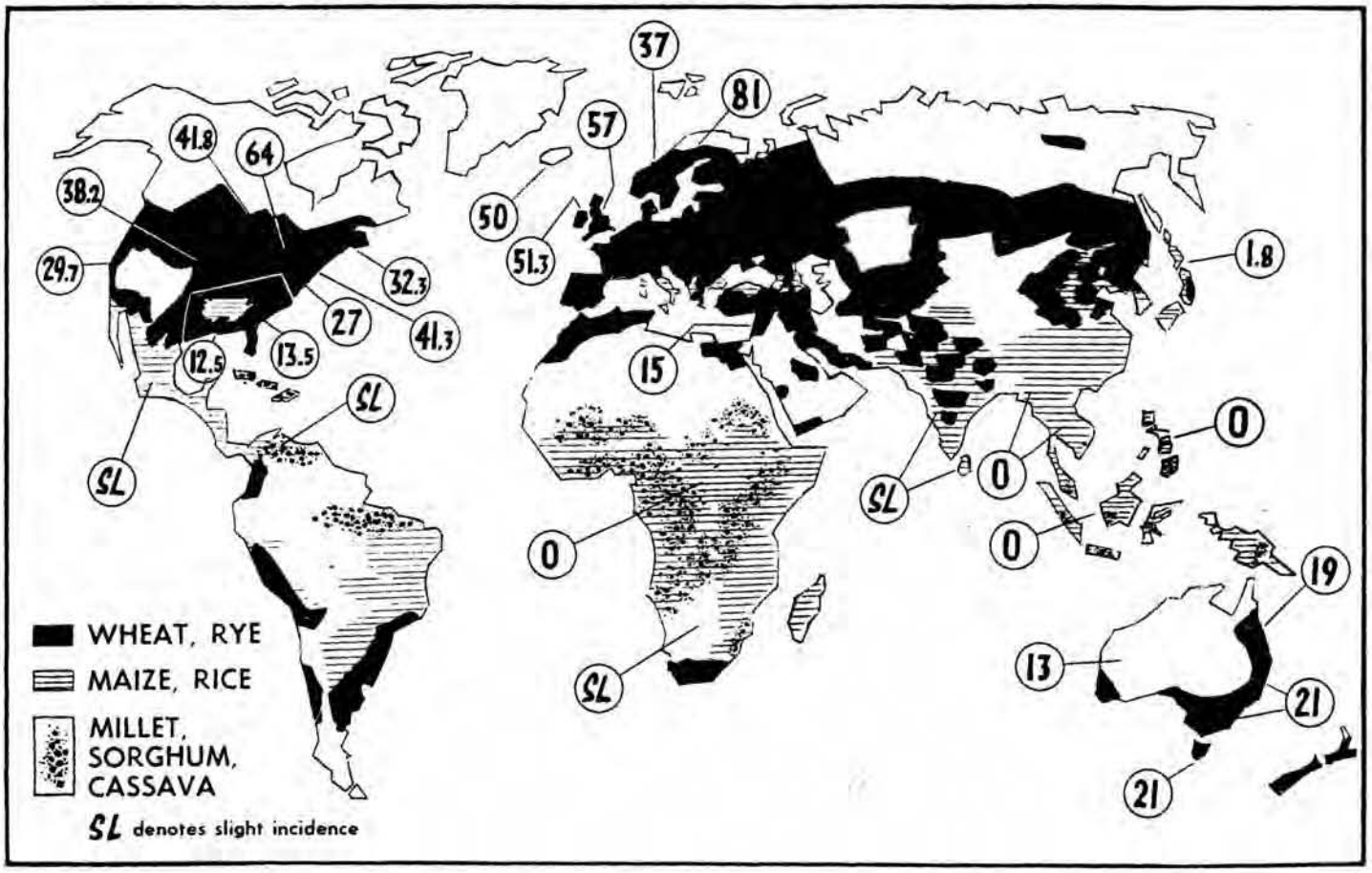
On this view the geographic pathology of obscure disorders studied by epidemiological means assumes new significance. It may be that geography of cereal cultivation may provide the key to their solution as shown in the accompanying world distribution of cereals and prevalance of multiple sclerosis.

Although the inter-diffusion of these cereals into various geographic zones is now considerable, it is true to say that Western European cultures everywhere are still based on wheat and rye staples, Asian, African and Central and South American (Indian) on rice, corn, millet and cassava.

It is suggested here that a productive field of inquiry would lie in investigating these obscure dis-

*Approx. 10,000 years.

Multiple Sclerosis per 100,000 of Population



orders (multiple sclerosis and rheumatoid arthritis) in the context of ecology both contemporary and in its historical perspective. These diseases show an apparent correlation with latitude and climate. This may be so because the geography of cereal cultivation from which the dietetic habits are derived — possibly important as aetiological factors in these diseases — is also dependent on latitude and climate [40]

On this basis epidemiological data of the prevalence of multiple sclerosis assume a pattern which has a meaning within the context of ethnic rather than geographic factors. These ethnic factors, it is suggested here, are related to the dietetic habits of Europeans and their descendants.

Thus, epidemiological data in Japan which disclosed negligible and equal incidence of multiple sclerosis in two widely separated cities, points to rice staple providing a common denominator. Similarly, Queensland, a tropical and sub-tropical State, has incidence of multiple sclerosis which does not differ greatly from those of the southern States of Australia. Perhaps wheat and rye provide a common denominator here.

I suggest that the type of cereal consumed could be more relevant to the incidence of multiple sclerosis than latitude and climate alone. This is well-exemplified by the relative incidence of multiple sclerosis which is eight times (if not more) as prevalent in Queensland among the wheat consumers, as it is in either southern or northern Japan, where rice is the staple.

The evidence that this indeed may be so is provided by a study of the possible role of food allergy in the pathogenesis of multiple sclerosis by Ehrentheil and his associates[31]. It is interesting to note that the report of this almost forgotten study was published in 1952, the year which also witnessed the discovery of the deleterious effects of gluten in coeliac disease made independently at the same time in Scotland and in Holland.

Ehrentheil and his associates found a high percentage of positive conjunctival reactions to rye and wheat in patients with multiple sclerosis as compared with the control group and significantly a reaction to rice occurred only in one patient.

As to rheumatoid arthritis, its incidence in non-Europeans has not been extensively studied, but in Japan, which occupies approximately the same latitude as Northern Europe, its incidence is about one-tenth that found in the old world[32].

Furthermore, the known incidence of rheumatoid arthritis in Brazil is only a fraction of that found in Europe and is mainly confined to the urban section of the population of European stock who are largely wheat consumers. The rural dwellers, predominantly of Indian descent, too poor to afford wheat, must subsist on corn (maize) and cassava and they rarely appear to suffer from rheumatoid arthritis, although osteoarthrosis is not infrequent among them. Of course, poverty could be the reason for failing to seek medical attention and consequently they would be excluded from surveys[33].

This idea of ethnic aetiology of rheumatoid arthritis based on dietetic habits derives further support from observations of the absence of rheumatoid arthritis in the indigenous Negro inhabiting tropical Africa. Thus in Liberia among 230 subjects studied serologically there was a high incidence of the rheumatoid factor, but not a single case of clinical rheumatoid arthritis was found among them[34]. Manioc, maize, and cassava are the staples of these people, and rheumatoid arthritis is thought to be absent among them in contrast to the wheat (and rye and oats) eating American Negro, who has a high incidence of this disease and apparently in this respect is indistinguishable from Caucasians.

Observations that Maoris, who frequently suffer from gout, have a much lower incidence of rheumatoid arthritis than New Zealanders of European race, are findings which have been recently confirmed but not interpreted[35].

These data, which cannot be explained on the basis of purely racial differences, assume meaningful significance within the premises of the ecological concept attempted by the present author. According to this concept, a partial adoption of European dietetic habits based on wheat staple by these indigenous populations would tend to produce rheumatoid arthritis among them but its incidence and severity would be much less than in Europeans.

Apparently to the semi-tribal Maori kumara (sweet potato) botanically Ipomea batatas is still more important than wheat as a staple[36] and this may explain a much lower incidence of rheumatoid arthritis among them.

The effects of nature and quantity of food supply surely must have an impact on the epidemiology of disease. Although our knowledge of the history of disease as it occurred in the antecedents of the existing European populations is very incomplete, in arthritis at least skeletal remains provide what permanent record is available to the fragmentary science of paleopathology.

In turning to paleopathology, it is necessary to draw attention of non-medical readers to an important distinction between rheumatoid arthritis discussed here, which is symmetrical, atrophic and tends to be centripetal in distribution, and the pathologically and pathogenetically distinct disorder referred to as osteoarthritis.

Postural, traumatic and other mechanical and possibly endocrinological factors are important in the pathogenesis of osteoarthritis. Paleopathology refers frequently to this disease as occurring not only in prehistoric man and hominids but also in large reptilian fossils such as Mesozoic Platecarpus (Mus. Nat. Hist. Kansas Univ.), a large swimming reptile of 100,000,000 years ago.

As has been rather humorously expressed by Karsh and his associate[37]: "In these parlous times, man loves to muse about the happier days when carefree creatures roamed the pristine earth in blissful ignorance of the aches and pains to come. For whatever solace it may bring to our worried age, it is unlikely that such an idyllic epoch ever existed. While the Proterozoic sponges of over 600,000,000 years ago may have been free of disease, this cannot be said of the Paleozoic forms that followed them. A far truer picture can be painted of grotesque reptilian monstrosities limping, not cavorting, through jungles and swamps to bathe

their sick joints in the warm muck of the natural spas that surrounded them. In this dismal setting arthritis started its invidious trek through time."

But in all these writings there is no positive evidence of a prehistoric atrophic, osteoporotic and symmetrical type of arthritis, which is the characteristic feature of rheumatoid arthritis as seen in modern conditions among the wheat and rye consumers of European descent.

The earliest archaeological discovery of rheumatoid arthritis in the human skeleton fulfilling modern criteria[38] is described by May[39] in an Egyptian mummy excavated by Sir Flinders Petrie. The famous archaeologist dated this skeleton 2750 to 2625 B.C. The next genuine discovery of skeletal remains showing this disease also comes from Egypt and is dated 1300 B.C. — the property of the Royal College of Surgeons[37].

Subsequently rheumatoid arthritis occurs with increasing frequency among Nubians, Romans and ancient Britons up to the present time.

Thus we find that, according to the records of paleopathology and archaeology, osteoarthritis goes back to the reptilian age and has harried man since the dawn of evolution; whereas rheumatoid arthritis, so common today, apparently did not exist before man first tamed the wild grasses and made them his food.

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