up to 6 hours on the first day and then at daily intervals up to 72 hours after the injection of ^{131}I-A.F.G.

RESULTS

In immunodiffusion tests ^{131}I-A.F.G. reacted only with human fibrin (fig. 1). The average biological half-life of ^{131}I-A.F.G. in three normal subjects was 2·7 days, and in a patient with acute thrombophlebitis of both legs it was 1·8 days.

The investigation to determine the normal distribution of labelled A.F.G. in controls found an increased accumulation during first few hours in the heart and liver and in the iliac and femoral blood-vessels; this was followed by a gradual decrease. Uptake of ^{131}I-A.F.G. by thrombi reached a maximum 48 hours after injection, as judged by the intensity of the scintigram. The difference in ^{131}I-A.F.G. uptake by thrombi and varicosities was also greatest 48 hours after injection. The uptake ratio was highest in those patients with thrombi, intermediate in those with varicosities, and lowest in those with normal veins.

In a woman in her sixties with recurrent thromboses, thrombophlebitis had started in the left leg 7 days before the injection of ^{131}I-A.F.G. The scintigram obtained 48 hours after injection accorded well with the clinical changes, in that an increased uptake of ^{131}I-A.F.G. and a well-defined outline of the thrombophlebitic areas of the enlarged varicosities of the left thigh and calf were demonstrated. The non-inflamed varicosities of the right leg were less well defined (fig. 2).

Extravascular deposits of ^{131}I-A.F.G. in fibrin were found in the patient who had a gangrenous foot, and the one with a fresh hand injury, the uptake of labelled A.F.G. being highest 48 hours after the injection.

DISCUSSION

Various radiolabelled agents,[1–6] including anti-fibrinogen antibody,[7] have been used to localise thrombi. However, the use of anti-fibrinogen antibody was restricted by its cross-reactivity with fibrin. The anti-fibrin antibody tested in the present study has the advantages of pronounced specificity for fibrin and the ability to detect both forming and formed thrombi. Our results suggest that ^{131}I-A.F.G. can also discriminate between acute thrombosis and chronic varicosities.

The most discriminant thrombus-to-normal or thrombus-to-varices ^{131}I-A.F.G. ratios in the veins of lower extremities were found 24 and 48 hours after the injection, thus indicating that this was the best time to scan for thrombi. Compared with the low rate of uptake in the heart cavities at 24 hours such an accumulation-rate in the blood-vessels implies that coronary thrombosis might be displayed by this method. Further, the observation that the 24-hour period after injection of A.F.G. is sufficient for the display of thrombi indicates that iodine-123, with its 13-hour physical half-life, could also be used as a radiotracer with A.F.G. The risk of sensitisation to rabbit immunoglobulins is a disadvantage of A.F.G.

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References at foot of next column

Hypothesis

SILICON, FIBRE, AND ATHEROSCLEROSIS

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Summary A logical argument can be made for the hypothesis that lack of silicon may be an important ætiological factor in atherosclerosis. As silicic acid or its derivatives, silicon is essential for growth. It is found mainly in connective tissue, where it functions as a cross-linking agent. Unusually high amounts of bound silicon are present in the arterial wall, especially in the intima. Various kinds of dietary fibre have been reported to be effective in preventing experimental models of atherosclerosis, reducing cholesterol and blood-lipid levels, and binding bile acids in vitro. Exceptionally large amounts of silicon (1000 to 25 000 p.p.m.) were found in fibre products of greatly varying origin and chemical composition which were active in these tests. Inactive materials, such as different types of purified cellulose, contained only negligible quantities of the element. It is concluded that silicate-silicon may be the active agent in dietary fibre which affects the development of atherosclerosis. Two out of three samples of bran also had relatively low levels, which could explain why bran does not lower serum-cholesterol. The fact that atherosclerosis has a low incidence in less developed countries may be related to the availability of dietary silicon. Two instances are presented where silicon is reduced by industrial treatment: white flour and refined soy products were much lower in silicon than—their respective crude natural products. The chemical nature of silicon in different types of fibre is not known. It could exist as orthosilicic acid, polymeric silicic acid, colloidal silica (opal), dense silica concretions, or in the form of organically bound derivatives of silicic acid (silanolates). Possible mechanisms of action are discussed.

INTRODUCTION

IN 1972 we demonstrated, by means of a plastic trace-element-sterile isolator system and highly purified

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aminoacid diets, that silicon (as silicic acid or its derivatives), is an essential element.[1] In rats fed silicon-deficient diets, supplements of metasilicate enhanced the rate of growth by 35%. Similar observations were made on chicks.[2] Silicon deficiency is accompanied by bone deformities.[3,4] The element is found mainly in connective tissue, where it functions as a cross-linking agent of the ground matrix.[5] Fractionation studies showed that it is bound to mucopolysaccharides, such as hyaluronic acid and chondroitin-4-sulphate, and also to collagen.[6] It appears to be present as an ester (or ether-like) derivative of silicic acid, forming -O-Si-O- bridges and thus contributing to the architecture and strength of connective tissue and membranes.[5] The silicon atom is eminently qualified as a cross-linking agent: it is a small atom with the same stereochemistry as carbon but with much greater rigidity in maintaining its bond angles. Unusually high amounts of bound silicon are found in the arterial wall, especially the intima.[7] In earlier work, Loeper and collaborators found that silicon levels were greatly reduced in atherosclerotic arteries. An inverse relation exists between the degree of atherosclerosis in the arterial wall and its silicon content.[8–10] More recently beneficial effects of silicate in drinking-water have been described on blood-lipid levels and cholesterol metabolism.[11,12] A coherent argument can thus be made for the hypothesis that lack of biologically available silicon in modern diets may play a part in the ætiology of atherosclerosis, and silicon may exert a protective effect against this disease.

The role of dietary fibre in the prevention of atherosclerosis and other chronic diseases has recently attracted attention.[13,14] The idea originated over 20 years ago from a comparison of diets and disease patterns in Africans and Westerners,[15–17] from findings in the U.S.A. of lowered serum-cholesterol levels in vegetarians,[18,19] and from a comparison of the diets of Italians and Americans, in whom small but significant differences in serum-cholesterol were related to pectin.[20] Earlier, the action of pectins in the human and dog intestine had been analysed, and changes in the metabolism and excretion of cholesterol had been noted.[21,22] More pronounced and consistent effects were observed under experimental conditions, as first described by Wells and Ershoff in 1961.[23] Rats, chicks, rabbits, pigs, and also primates, including man, were used, and not only cholesterol and blood-lipid levels but also experimental models of atherosclerosis were found to be beneficially affected. Recently, in-vitro bile-acid binding has been applied as a method to study the action of fibre-containing products. Comprehensive reviews are available.[24–27]

"Dietary fibre" is poorly defined chemically. It designates constituents of food which are resistant to digestion. This comprises not only cellulose but also hemicelluloses, pectins, other polyuronides, gums, mucilages, lignin &c. Many studies have been published on the effects of these products on blood cholesterol and lipid levels and on experimental models of atherosclerosis. Cellulose, per se, was without influence on serum-cholesterol in all tests except one.[28] Indeed, in some of these studies cellulose functioned as a filler or placebo.[29,30] Since only certain types of fibre are effective under various experimental conditions, it seems inappropriate to speak about "fibre" in general as a hypocholesterolæmic agent.[31]

We have analysed a variety of products belonging to the category of dietary fibre. The results indicate that an exceptionally high amount of silicon is a common denominator of seemingly unrelated components of dietary fibre and other products which have been reported to be effective in lowering cholesterol and lipid levels, preventing experimental atherosclerosis, or binding bile acids in vitro.

METHODS

Silicon analyses were performed after ashing by sodium-carbonate fusion in platinum crucibles, using the colorimetric method of Baumann.[32] High-purity chemicals, plastic laboratory ware, and silicon-free water were used throughout. Precautions were taken to eliminate the possibility of contamination by dust. Results are expressed as parts per million (P.P.M.) of silicon per dry-weight.

RESULTS

Various kinds of purified cellulose were very low in silicon (see table, nos. 1–3), and cotton, considered the purest natural form of cellulose, contained only 120 p.p.m. Other samples of fibre (except two specimens of bran) had exceedingly high levels, despite their diverse biological and geographical origins. Values ranged from approximately 1000 to over 25 000 p.p.m. These amounts are quite large compared to those in tissues and parenchymal organs, which are normally in the range 2–30 p.p.m.[33] Except for lungs and lymph-nodes, only connective tissue often exceeds 100 p.p.m.[1]

SILICON IN DIETARY FIBRE

Sample	Silicon (p.p.m. of dry weight)	Sample	Silicon (p.p.m. of dry weight)
1. Cellulose powder, Solka-Floc*	6	14. Wheat bran‡	348
2. Cellulose, Whatman F-11	6	15. Wheat bran§	229
3. Filter-paper, Whatman No. 1	50	16. Wheat flour (65% extraction)§	21
4. Cotton, pure, sterile	116	17. Soybean meal¶	1680
5. Sugar beet pulp†	23 110	18. Soya fluff‖	80
6. Sugar cane pulp†	11 270	19. Nutrisoy flour**	93
7. Alfalfa‡	12 740	20. Citrus pectin N.F.*	1130
8. Rice straw‡	27 300	21. Lemon pectinin††	1100
9. Rice hulls‡	22 500	22. Na-polypectate‡‡	1040
10. Oat hulls†	16 910	23. Na-pectate, enzymatically de-esterified††	1100
11. Oat straw‡	7 140	24. Guar gum*	1420
12. Wheat straw†	12 240	25. Curry powder§§	1800
13. Wheat bran†	1 720	26. Chondroitin-4-sulphate¶¶	1175

*Dr P. Griminger, Rutgers University, New Brunswick, New Jersey.
†Dr D. Kritchevsky, Wistar Institute, Philadelphia, Pennsylvania.
‡Kruse Grain & Milling, El Monte, California; samples washed twice with 1:1 EtOH-$CHCl_3$ solution before analysis.
§American Institute of Baking, Chicago, Illinois.
¶Cargill Inc., Minneapolis, Minnesota; solvent-extracted, 48·5% protein.
‖E. C. Young, Co., Los Angeles, California.
**Archer Daniels Midland Co., Los Angeles, California.
††Dr R. McCready, Western Regional Laboratories, Berkeley, California.
‡‡Sunkist Growers, Ontario, California.
§§Spice Islands, San Francisco, California.
¶¶Institute of Atherosclerosis Research, Los Angeles, California.

Some of the items analysed (see table) were obtained from other institutes, where they had been assayed for various effects: crude fibre products (nos. 5, 6, 10, 12, and 13) have been studied by Story and Kritchevsky for their potential to bind bile-acids in vitro.[34] All were effective, except for wheat straw, and all showed high amounts of silicon. The same authors have found curry powder to be quite active in bile-acid binding;[35] a commercial sample (no. 25) showed 1800 p.p.m. of silicon. The National Formulary pectin (no. 20) and the guar gum (no. 24), in both of which high amounts of silicon were detected, have been used by Griminger and Fischer in studies of cholesterol levels in chicks.[36] In five other citrus pectins not shown here values ranged from 1100 to 2590 p.p.m. We reported previously that pectin contains large amounts of silicon. Stability tests indicated that it is present as an organically bound form of silicic acid, an organosilicate.[5] However, commercial pectins are often contaminated with microscopic and colloidal silica. Chemical modification of pectin did not significantly alter the silicon levels found (nos. 21–23). The sample of chondroitin-4-sulphate (no. 26) is representative of many similar specimens studied in our laboratory. Extensive clinical trials showed beneficial effects on atherosclerosis.[37] A large amount of silicon was found, in accordance with our previous report, in chondroitin sulphates and other glycosaminoglycans.[5]

DISCUSSION

Different kinds of dietary fibre might affect chronic diseases through a variety of mechanisms. Fibre might change fatty-acid absorption, bacterial flora, formation of volatile fatty acids, intestinal-transit time, and consistency of fæces. It also counteracts toxic effects. Its mode of action in atherosclerosis could clearly be different from the mechanisms which have been invoked in the prevention of other diseases—e.g., diverticulitis and cancer of the colon.

Large amounts of silicate-silicon (1000–25 000 p.p.m.) are present in very different kinds of dietary fibre which lower serum cholesterol and lipid levels or prevent experimental atherosclerosis or bile-acid binding. Conversely, types of fibre which are inactive in such tests (e.g., cellulose) contain only negligible quantities of the element. The influence of natural fibre on atherosclerosis obviously does not depend on cellulose itself, for fibre products containing no cellulose are also effective in various trials. Since a high silicon content is characteristic of the active products, silicate-silicon may be the crucial ingredient in these materials.

The much lower incidence of atherosclerosis in less developed parts of the world than in industrialised areas may be related to the availability of silicon in the diet. Skin, cartilage, tendon, and other parts of animal origin which are rich in silicon may be used less efficiently for human consumption in developed countries; in addition, the intake of fibre of plant origin is reported to be much lower. Industrial refinement can greatly reduce the amount of silicon in foods: samples (nos. 15 and 16) of bran and wheat flour were prepared by carefully controlled milling of a specific lot of wheat. 65%-extraction flour contained less than 10% of the silicon found in bran. Soybean meal (no. 17), a source of fibre which reduces blood-lipids and experimental atherosclerosis,[38] was high in silicon, but two refined soybean preparations for human consumption (nos. 18 and 19) contained very little of the element.

Bran samples of different origin (nos. 13–15) varied significantly in silicon content, two out of three specimens having low values. Such differences may be related to the kind and origin of the grain and to differences in the milling process. They could account for discrepancies in the results obtained with bran by different investigators.[39 40] Whereas some authors have seen effects on blood-lipids in experiments with bran supplements, others have found bran ineffective in lowering serum-cholesterol, despite its popularity. Indeed, there appears to be no report which states that bran lowers serum-cholesterol levels *in man*. There are similar inconsistencies in the reported effects of cellulose. Whereas the purified preparations analysed by us were very low in silicon, other cellulose specimens, of different origin, may contain higher amounts.[2]

The chemical nature of silicon in the various types of fibre investigated here is not exactly known. In plants it exists as orthosilicic acid, polysilicic acid, colloidal silica (opal), and also as dense silica (SiO_2) concretions (phytoliths). Hard woods may contain over 0·5% of SiO_2.[41] Organically bound forms of silicic acid also play a part—for instance, in straw, where galactose has been implicated as the site of silicate binding.[42] Various forms of silicon in different categories of fibre obviously may differ in availability. Different forms of silicic acid and polymerised silica (SiO_2) vary in their absorbability in the gastrointestinal tract.[43] In our experience the organosilicates—i.e., esters of silicic acid—appear to be utilised best for growth in the rat.[7]

Several mechanisms could be involved in beneficial effects of silicate-silicon on atherosclerosis:

1. Various forms of polymeric silicic acid or silica could be the site of bile-acid binding in the digestive tract, which would enhance the elimination of metabolic end-products of cholesterol; binding of cholesterol itself could also play a part. This concept is supported by studies which showed that addition of silicic acid to drinking-water caused a significant reduction of serum cholesterol and lipid levels, enhanced excretion of tritium-labelled cholesterol and its conversion products in the fæces, and reduced the uptake of labelled cholesterol in liver, spleen, and kidney.[11 12]
2. Silicic acid or other biologically active forms of silicon (organosilicates) could be absorbed and function in the organism as essential constituents of connective tissue. They would thus contribute to the integrity and stability of the arterial wall.
3. An activated form of silicic acid could participate directly in the intermediary metabolism of steroids and bile acids.

The observations reported here may also be related to the water factor—i.e., the constituent of hard water which seems to exert an inhibitory effect on coronary heart-disease.[44 45] We have found an inverse relation between silicic acid in drinking-water and the prevalence of coronary heart-disease in Finland,[46] suggesting once again that lack of silicon may be an ætiological factor in atherosclerosis.

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References overleaf

Reviews of Books

Influenza

The Viruses and the Disease. Sir CHARLES H. STUART-HARRIS, F.R.C.P., University of Sheffield, and G. C. SCHILD, PH.D., National Institute for Biological Standards and Control, London. London: Arnold. 1976. Pp. 242. £12.

THE influenza virus is the most intensively studied of all the viruses that afflict mammals. It has provoked a large and still increasing flood of literature. And yet the disease reigns triumphant, and epidemics come and go in pigs, horses, birds, and, especially, in man, with little hindrance from general preventive measures and from specific vaccines. In general, the reasons for this are poorly understood by doctors. They have a vague idea that influenza vaccines are not much good, and that the capacity of the virus for change has defeated the virologists and epidemiologists. This relatively short book could do much to correct many misapprehensions, by enabling practising physicians to approach the protection of their patients from a position of knowledge. Influenza vaccines do function efficiently against homologous viruses, although for only a relatively short period. If they and the epidemic viruses are suitably matched and if they are available in the right quantity at the right time, they can do as much for the population as most other virus vaccines. The advantage of this book is that it represents a fusion of applied and academic thought. Scientists and physicians have tended to work on this subject in seclusion, with the hope, as with parallel lines, of an ultimate rendezvous at infinity. But much of the basic knowledge available on the viruses can already be applied to the prevention of the disease or to an understanding of its mechanisms, although effort and study are required to achieve this. The book describes authoritatively the complex properties of the influenza viruses, what is known about their antigenic make-up, and why vaccines have often been judged ineffective. The natural history and epidemiology of the disease are interestingly described, and sections have been added on disease processes, immune mechanisms, chemotherapeutic measures, and laboratory techniques. That one is left with the feeling that so much more remains to be discovered is in itself a tribute, and the book can be warmly recommended as basic reading for all those concerned in the prevention, treatment, and control of influenza, and for those who are anxious to make vaccines work.

Recent Advances in Clinical Virology I

Edited by A. P. WATERSON, F.R.C.PATH., Royal Postgraduate Medical School, University of London. Edinburgh: Churchill Livingstone. 1977. Pp. 200. £9.75.

IN virology today there are two main factions—one concerned primarily with investigation of viral virulence and disease spread, the other devoted to the study of viral substructure properties, ecology being of less import. The former group, sometimes believing themselves overshadowed, now tend to identify their interests as clinical, though on occasion this may sound more euphonic than precise. To their support has come the first of this new series on advances in clinical virology. Edited by Professor Waterson, which should provide some guarantee of merit, the volume contains twelve reviews on current topics relating to infectivity. These are of varying relevance to the practice of clinical virology, but important enough to justify selection. The contents range over problems of vaccination, the encephalopathies, and some individual illnesses. The chapters on vaccines are concerned with cytomegalovirus and measles, rubella, and rabies viruses. The encephalopathies take in subacute sclerosing panencephalitis (S.S.P.E.), Creutzfeldt-Jakob disease, scrapie, and the progressive multifocal leucoencephalopathy associated with the still enigmatic group of papovaviruses. There are also chapters on herpes encephalitis, Lassa fever, viral gastroenteritis, and Coxsackie virus infection of the heart. Every chapter is the work of an expert. From relative brevity on Lassa fever to lengthy coverage on S.S.P.E. they reflect the degree of complexity of the different topics. They also provide numerous references. Where electron micrographs are included reproduction is fairly good, though there is some loss of fine detail. Despite editorial words on the benefit of interchange between human and veterinary virology the book is predominantly medical in outlook. The comparative virology of gastroenteritis is but a shadow on the scene and the impression is that scrapie is there for its similarity to Creutzfeldt-Jakob disease as much as in its own right. Such things do not necessarily detract from the merits of the book, but if there is to be intermingling with the veterinary profession there must be a more equable distribution of topics in future volumes. Caution in giving rabies vaccine intradermally may be needed, and there is no mention of Marburg disease, but these are quibbles. This book can be recommended as a worthwhile introduction to a new series.

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