

no practitioner will henceforward be justified in giving advice on dietary matters, whether such advice is designed to increase or to diminish a patient's diet in respect of particular food constituents, unless he has a copy of this report—not in his upper bookshelves but on the desk of his consulting-room.

#### ESTIMATIONS OF VITAMINS IN MARGARINE

Margarine is now compulsorily vitaminized with vitamins A and D. The estimation of these in margarine is constantly engaging research chemists, and two papers on the subject were recently read before the Society of Public Analysts and Other Analytical Chemists. The estimation of vitamin A depends upon spectrometric tests of a highly technical character, but for vitamin D the spectrometric and chemical methods are not suitable, and recourse is made to a biological method. Hitherto what is known as the "line" test has been employed, a test based on the measurement of calcification in the bones of the young rat. In the newly weaned rat the shaft of the bone of the extremities is separated from the cap by a width of cartilage, and calcification normally takes place as the animal grows older. If, before calcification is complete, the rat is fed on a deficiency diet, the process ceases. One animal of a pair which have been deprived of vitamin D is then made to receive a certain prescribed amount of the vitamin per day as the International Standard, the other receiving a sample of margarine thought to contain about an equivalent amount of the vitamin. At the end of ten days both animals are killed, the leg bones dissected out, hardened in formalin, and stained with silver nitrate, and the new lines of calcification in the animals is precisely measured and comparison is made. This method has proved satisfactory for margarines having a potency of about one international unit per gramme. With lower-potency margarine, however—say those of 0.1 unit per gramme—or winter butter the results from these assays are liable to be falsified by the effect of the fat. To assay low-potency margarine the more sensitive bone-ash method has been adopted, and this was described in some work from the Unilever Research Laboratories by Dr. H. Wilkinson and two collaborators at the meeting of the society above mentioned. The bone-ash test, unlike the "line" test, is a prophylactic method. Newly weaned rats are again taken in pairs, one of each pair being given vitamin D daily according to the dose of Standard and the other the test substance. At the end of three weeks the rats are killed and the bone-ash content of the dried hind-leg bones computed. The bone-ash percentage in the newly weaned rat may be roughly 45, and may fall to 20 after three weeks' deprivation of vitamin D. This test has been found to work perfectly well with dosages of one-sixteenth of an international unit of vitamin D per day. One curious result on comparing the "line" test with the bone-ash test is that in every case the value elicited (expressed as the ratio of the potency of the substance tested to the potency of the international standard) is lower than that obtained by the "line" test. The "line" test measures a purely localized reaction, whereas the bone-ash test, which is much more sensitive, measures a generalized reaction. Dr. Wilkinson and his co-workers have lately transformed the bone-ash test from a prophylactic to a curative test, and again the same quality of results has emerged. In the same rats, after the prescribed period, the front legs have been dissected out for the "line" test and the hind legs ashed for the bone-

ash test, and again the values are consistently lower for the latter test than for the former. It emerges from this work that ordinary margarine of a potency of about one unit per gramme can be assayed quite satisfactorily by the "line" test, but that materials of lower potency are probably best assayed by the bone-ash method, in which case values lower than those obtained by the first method must be expected.

#### PYRUVIC ACID IN VITAMIN B<sub>1</sub> DEFICIENCY

The normal amount of pyruvate in human blood is about 0.5 mg. per 100 grammes.<sup>1</sup> During exercise this amount increases considerably, and the higher level may be maintained or even increased still further at the end of half an hour's rest after the exercise.<sup>2</sup> If, however, vitamin B<sub>1</sub> is injected intravenously before the exercise is taken, light exercise may or may not be followed by an immediate increase in blood pyruvate. Heavy work may bring about a large increase in blood pyruvate, accompanied by clinical manifestations resembling those of fulminating beriberi, but still heavier work may be unaccompanied by these symptoms if the subject is adequately supplied with vitamin B<sub>1</sub>. The blood pyruvate of vitamin-B<sub>1</sub>-deficient subjects can be raised by exercise to the level found in patients with fulminating beriberi. Similar high values have been observed in normal subjects exercised to exhaustion. Initial values may be restored in normal subjects by resting for less than an hour. In vitamin-B<sub>1</sub>-deficient subjects recovery after exercise is delayed. Thus vitamin B<sub>1</sub> seems either to prevent the formation of the excess pyruvate or to help in its dispersal. It has been suggested that the amount of pyruvate in the blood before and after exercise and again after half an hour's rest would afford a means of detecting latent vitamin B<sub>1</sub> deficiency. The fate of the pyruvic acid of the blood has also been investigated.<sup>3,4</sup> It is excreted in increased amounts in the urine after exercise, but when pyruvate is injected into the blood stream it does not pass wholly into the urine. Some of it is apparently changed into a non-glucose-reducing substance and lactate, which afterwards give rise to glucose. About 2 to 3 per cent. of it is found in the muscles eight minutes after injection, and there is little or no change then in muscle lactate or glucose. It is almost certainly concerned with the regeneration of carbohydrates, but in what way is by no means clear yet.

#### DECLINE IN MORTALITY FROM RHEUMATIC HEART DISEASE

A recent report of the Registrar-General for England and Wales<sup>1</sup> shows that in recent years there has been a substantial decline in the mortality attributed to rheumatic fever. In the three years 1925-7 the death rates per million living at ages 5 to 15 were 75 for males and 90 for females; in 1937 they were 41 and 49. At ages 15 to 25 the death rates were 49 for males and 60 for females in the earlier period, and 25 and 33 in 1937. Broadly speaking, the mortality rate has fallen by 50 per cent. in ten years. A similar trend is reported from the United States by O. F. Hedley.<sup>2</sup> As most deaths from heart disease at ages 5 to 24 years are the result of rheumatic infection he adopts the recorded mortality of the former as an index of the trend, and racial and geographical distribution, of the latter. The annual death rates during 1930-6 were, he finds, less than the corresponding rates during 1922-9 in every section of the country and in every

<sup>1</sup> *Biochem. J.*, 1939, **33**, 1525.

<sup>2</sup> *Ibid.*, 1538.

<sup>3</sup> *Ibid.*, 1544.

<sup>4</sup> *Statistical Review for 1937, 1940*, Text, H.M. Stationery Office. (3s. 6d. net.)

<sup>5</sup> *U.S. publ. Hlth. Rep.*, Wash., 1939, **54**, 2271.

State. In the United States as a whole the mortality rate was 192 per million living at ages 5 to 24 in 1922-9 and 139 per million in 1930-6, a reduction of nearly 30 per cent. (His basis, it will be noted, is a wider one than the Registrar-General's, the latter's figures for rheumatic fever including heart diseases only when the heart affection is designated as "acute [or subacute] rheumatic" on the death certificate.) While this improvement is a source of satisfaction it must not be forgotten that heart disease remains at these young ages one of the principal causes of death. The reason for the improvement is also obscure, for the cause of rheumatic fever is still unknown and we have no proved methods of preventing it, though with earlier detection and treatment the cardiac damage is probably more frequently averted. Hedley concludes that it is certainly not a mere statistical bookkeeping change, and puts forward a number of factors that may be relevant. It is the impression of many of the older clinicians, he says, that rheumatic fever may to-day be becoming milder. This would be on a par with the experience of scarlet fever, but only pushes the search for an explanation one stage further back. He boldly enters a controversial field in suggesting that the widespread removal of diseased tonsils may have been important. The fall in mortality has, of course, been associated in time with an improving standard of living and changes in diet, but so far attempts to incriminate dietary deficiencies have been unsuccessful. The incidence of rheumatic fever has, however, been reported to be higher in the poorer classes, and Hedley finds the mortality from heart disease appreciably higher among young negroes than among the whites, the economic position of the former being, on the average, certainly less favourable. On the other hand, mortality continued to decline during the years of economic depression. Other possible influences lie in improvements in the housing of the population and in the generally better child hygiene of to-day, with less overcrowding and less risk of infection with smaller families. The value of identifying the cause, or causes, of the fall in mortality would be, as Hedley points out in this preliminary report, that we might then be able still further to accelerate the decline.

### FLUOROSIS

Small quantities of fluorine are usually regarded as essential for maintaining normal function. During the past ten years, however, evidence has accumulated to show that a slight excess of fluorine is very injurious to the teeth; indeed, it is now doubtful whether this element is essential at all. Evans and Phillips<sup>1</sup> maintained rats for five generations on a diet containing only traces of fluorine (not more than 50  $\mu$ g. of fluorine per kilo body weight per day), and found that the addition of more fluorine did not improve the health, while an intake of about 5 mg. per kilo body weight per day caused bleaching of the teeth. Mottled teeth have been endemic in certain areas of the United States for some years, and in 1918 McKay pointed out that in Andover (South Dakota) the disease was associated with the use of water from artesian wells. It was in 1931 that Smith and Churchill established that mottling of the teeth was due to the presence of fluorine in the water. In extensive observations in a number of areas Dean and McKay<sup>2</sup> have found that where there is a concentration of one part per million of fluorine in the water 10 per cent. of the

children have mottled teeth, and where the concentration is two parts per million the teeth of 50 per cent. of the children are so affected. Further, a concentration of 5 parts per million causes nearly a 100 per cent. incidence of mottled teeth and a 20 per cent. incidence of severe effects. The mottling appears on the teeth between the ages of 6 and 12 years, and the injury is permanent. Dean and McKay have shown that no fresh cases occur in the locality after a change over to a fluorine-free water supply; they point out, however, that it takes eight years for this to become apparent in the community. An otherwise laudable desire to improve drinking-water supplies by substituting artesian wells for surface water has been largely responsible for the increase in the incidence of this dental disease. Surface waters rarely contain fluorides, which, however, occur in about 85 per cent. of igneous rocks; thus water from deep wells may have a high fluoride content. Fluorosis is recognized as occurring in all continents. Pierce<sup>3</sup> points out that it is a widespread trouble among domestic animals, which in North and South America have mottled teeth like the children. Along the North African coast a disease of the teeth and bones of horses and cattle termed "darmous" is now recognized as being caused by fluorine. Cattle are also subject to special dangers from dust from various factories, particularly superphosphate factories. Natural phosphate deposits contain fluorine, and fertilizers made from rock phosphate may thus contain a considerable quantity of the element.

### SAFETY ZONES

Probably with some presentiment of coming events affecting their three countries the Netherlands and the Belgian and Luxembourg sections of the International Law Association met in Brussels in April, and after a discussion in which many took part adopted a draft convention for the creation of zones of security in which the non-combatant population, especially children, might find shelter against aerial attack. The assembly were informed of the results of similar endeavours in recent wars, especially the zone of security in Shanghai for the civil population, in which 300,000 persons had found shelter during bombardment, and the measures in Madrid and Bilbao during the Spanish civil war. It was also stated that France and Germany had been engaged in obtaining mutual assent to measures for the immunity of certain hospital towns intended for the sick and wounded. A committee was appointed under the presidency of M. Devèze to continue propaganda in favour of the creation of such zones of security and to secure the adhesion of Governments to the draft convention. It will be recalled that at the International Red Cross Conference held in London in 1938 it was agreed to urge all Governments to arrange, in areas liable to be endangered by any military action, for the evacuation of women and children into zones of immunity under Red Cross protection. This was the unanimous resolution of the fifty-four National Red Cross Societies. The same conference carried a step further the long-debated question of hospital towns, and later, in October, 1938, a committee of military and legal experts met at Geneva to draw up suggestions for a convention for the establishment of hospital or sanitary zones in time of war. Representatives of the British, German, Belgian, and Polish Governments were on that committee. The proceedings seem to have a far-away sound now that "total war" is upon us.

<sup>1</sup> *J. Nutr.*, 1939, 18, 353.

<sup>2</sup> *Amer. J. publ. Hlth.*, 1939, 29, 590.

<sup>3</sup> *Nutr. Abstr. Rev.*, 1939, 9, 253.

### MORGAGNI'S SYNDROME

In 1761 Morgagni was the first to record a number of conditions, some rediscovered later, such as the form of cataract and the small "hydatid" which bear his great name. But this is not all, for he reported hyperostosis of the inner table of the skull associated with virilism and obesity, which Henschen<sup>1</sup> in 1927 called "Morgagni's syndrome." Hemphill and Stengel<sup>2</sup> have now given a detailed account of three such cases, one with necropsy, with valuable observations on the histology of the bony, cerebral, and endocrine changes, and a review of the subject. The syndrome consists of diffuse hyperostosis of the vault of the skull, especially of the frontal and parietal parts of the calvarium, with nodular frontal endostoses, but without evidence of activity; diffuse degeneration, not senile, of all the elements of the cerebral cortex in the frontal and to a less degree of the parietal regions; in the anterior pituitary increased numbers of eosinophil cells and the presence of small eosinophil adenomas; signs of activity in the parathyroids; and some atrophy of the thyroid which may be correlated with obesity. Although with wise caution Hemphill and Stengel do not insist on a resemblance to acromegaly in the pituitary eosinophilia, and in the occasional combination of cutis verticis gyrata or bull-dog scalp with acromegaly, the polyglandular endocrine manifestations in Morgagni's syndrome are paralleled to some extent by those in acromegaly.

### TOXOPLASMIC ENCEPHALOMYELITIS

In 1937 Wolf and Cowen<sup>3</sup> drew attention to parasitic form of human encephalomyelitis due to an organism resembling the *Encephalitozoon cuniculi* or, alternatively, *Toxoplasma*. The disease was identified in a newborn infant, and it appears certain that the infection was acquired *in utero*. Pathologically the central nervous system showed a disseminated granulomatous meningo-encephalitis, the optic nerves and retinae being also involved. The organisms were demonstrated in the stained sections, but in the absence of cultural and transmission experiments it was not possible to identify them with certainty. In 1938 Wolf and Cowen<sup>4</sup> reviewed five other cases from the literature in which the morphological features were similar. By this time they had had further opportunities of studying the appearances of a mouse strain of *Toxoplasma* in sections of fixed tissue, from which it was concluded that the morphological differences in such preparations between this organism and *Encephalitozoon cuniculi* were extremely slight. On account of the histological resemblance between the human disease and experimental toxoplasmosis in rabbits they inclined to the view that the human disease might turn out to be an encephalomyelitis due to *Toxoplasma hominis*. Wolf, Cowen, and Paige have now confirmed this view as a result of their investigations of a fresh case. The description<sup>5</sup> of the clinical and pathological features in this new example agrees in all essential respects with the original. In a separate report<sup>6</sup> they present the results of the inoculation of infected cerebral material into the brains of rabbits, rats, and newborn mice. Almost all of the rabbits and mice, but none of the rats, developed a disseminated meningo-encephalitis characterized by focal

inflammation, necrotizing and productive lesions in which parasites were identified. Both the lesions and the parasites were closely similar to those observed in the human material. Parasites were also found in similar lesions in a number of other organs. The disease proved to be transmissible in series and was identified as a toxoplasmosis by the morphology of the parasite, the character of the lesions, and the results of cross-immunity experiments. *Toxoplasma* has a wide-spread geographical distribution and is pathogenic for a wide variety of hosts, but its natural mode of transmission is unknown. By what means an infant can be infected *in utero* while the mother remains apparently healthy is an interesting conundrum.

### PHARMACEUTICAL RESEARCH

The annual report of the research departments of the College of the Pharmaceutical Society records activities in a wide field. The record is particularly creditable because the departments have been scattered by evacuation. In spite of this difficulty research has been carried on in such subjects as pharmaceutical chemistry, pharmacy, biological standardization of drugs, and nutritive products. The range of subjects investigated is very wide and includes the synthesis of new acridine antiseptics, improvements in the biological standardization of vitamins and hormones, and the measurement of the disintegration rate of compressed tablets. The nutrition laboratory has measured the relative activities of calciferol (vitamin D<sub>2</sub>) and vitamin D<sub>3</sub>, which is identical with that occurring in fish-liver oils. The two substances were found to be equally potent, weight for weight, both on rats and on children. Calciferol had been found to be much less potent than vitamin D<sub>3</sub> when tested on chickens, and this fact raised doubts about the therapeutic value of calciferol. It is satisfactory to learn that this difference does not exist in the case of human subjects.

### NOTICE TO CORRESPONDENTS

The need for strict economy in the use of paper for all purposes was emphasized by the Control of Paper Order made by the Ministry of Supply, which came into force last month. In view of the restrictions now imposed on the use of paper, and the increase in the rates of postage which came into operation on May 1, it will no longer be possible to acknowledge the receipt of letters and memoranda, etc., offered to the *British Medical Journal* for publication. The space devoted to correspondence has had to be curtailed, and readers are urged once again to be concise in all communications addressed to the Editor.

The next session of the General Medical Council will open on Tuesday, May 28, at 2 p.m., when the President, Mr. H. L. Eason, C.B., C.M.G., M.S., will take the chair and deliver an address.

News has been received from Southern Rhodesia of the death of Dr. D. Campbell Watt, formerly of Pietermaritzburg, a Vice-President of the British Medical Association.

We regret to announce the death at Exmouth in his seventieth year of Mr. L. B. Rawling, F.R.C.S., consulting surgeon to St. Bartholomew's Hospital.

<sup>1</sup> Henschen, F. (1927). *Morgagni's Syndrome*. Jena.  
<sup>2</sup> Hemphill, R. E., and Stenzel, E. (1940). *J. ment. Sci.*, 85, 341.  
<sup>3</sup> *Bull. neurol. Inst. N.Y.*, 1937, 6, 306.  
<sup>4</sup> *Ibid.*, 1938, 7, 266.  
<sup>5</sup> *Amer. J. Path.*, 1940, 15, 657.  
<sup>6</sup> *J. exp. Med.*, 1940, 71, 187.