were shown round the various collections of books and exhibits, including the new American Room, which now contains a valuable collection from the library of Dr. Francisco Guerro and is destined to become an important centre for American studies.

Research Fund Committee to conclude that continuation of the *History* by other scholars on the lines envisaged by the author would not only be difficult but quite impossible.

ARTHUR S. MACNALTY.

Nova et Vetera

SIGERIST'S "HISTORY"

In 1947 Professor Sigerist retired from his chair at Johns Hopkins University to Pura, near Lugano, in his native Switzerland, to write a comprehensive eight-volume *History of Medicine*. This great project was aided financially by Yale University, which appointed him a non-resident research associate. Volume I—*Primitive and Archaic Medicine*—appeared in 1951 and was accorded an enthusiastic reception. The titles for the remaining volumes were: II—*Early Greek, Hindu and Persian Medicine*; III—*Medieval Medicine*; IV—*Renaissance Medicine*; V—*The Seventeenth Century*; VI—*The Eighteenth Century*; VII and VIII—*Medicine from the Industrial Revolution to the Second World War*.

Of these the second volume alone was planned. It is now published in an incomplete form,* for before his death in 1957 Sigerist was able to analyse only the early periods of Greek, Indian, and Persian medicine. His knowledge of Sanskrit and his reading of the *Rigveda* gave him a high opinion of Vedic medicine, which was a combination of religious, magical, and empirical views and practices. He observes in his introduction that "Western and Indian Medicine were closely related and equally effective not only in antiquity but also in the Middle Ages." Unfortunately, death prevented him from developing this theme.

The book, admirably produced and illustrated, with a portrait of Sigerist, a preface from the late Professor John F. Fulton, and an editorial introduction by Professor Ludwig Edelstein, is a masterly analysis of the development of medicine in antiquity. Beginning with "Archaic Medicine in Greece," Sigerist recounts in detail the medical features of the *Iliad* and the *Odyssey*; he then discusses the cult of Asclepius with its bearing on religion and legend, followed by an interesting account of pre-Socratic philosophers—including Pythagoras, Philolaus, Democedes, Alcmaeon, Empedocles, and Democritus—and early medical schools. "Hindu Medicine" and "Medicine in Ancient Persia" follow. In the last section the author returns to Greece to describe the "Golden Age of Greek Medicine," with a careful appraisement of Hippocrates and the "Collection of Hippocratic Writings."

We must not deplore too greatly that Sigerist did not live to complete his *History*. In the two published volumes he has bequeathed much fresh learning and wisdom to mankind. Only Sigerist with his profound knowledge of historical medicine and of languages both ancient and modern could have written them. It was, therefore, a wise decision of the Henry E. Sigerist

**A History of Medicine.* Volume II: *Early Greek, Hindu, and Persian Medicine.* By Henry E. Sigerist. (Pp. 352+xvi; illustrated. 75s.) New York and London: Oxford University Press. 1961.

To-day's Drugs

Agranulocytosis after Hydrochlorothiazide

Since the introduction of chlorothiazide as an oral diuretic four years ago there have been a number of toxic reactions reported, not only with chlorothiazide itself but with the many related compounds showing similar activity. Among the milder symptoms are nausea and epigastric discomfort. Dizziness, weakness, and paraesthesiae have also been reported, as well as the usual allergic responses and skin eruptions. Less common toxic effects are skin photosensitivity, hyperuricaemia, and hypoglycaemia. The clinical signs and symptoms of electrolyte imbalance fall into a somewhat different category, since they are a consequence of the action of the drug on the blood chemistry which is associated with its therapeutic efficacy. In some patients a hypochloraemic alkalosis occurs due to excessive excretion of chloride and to this is often added an excessive excretion of potassium ions. Such imbalance is more likely to occur in patients on long-continued administration of the drug, and can usually be corrected by the administration of potassium chloride. Under the heading of serious toxic reactions come the blood dyscrasias. There are a number of records of thrombocytopenic purpura and agranulocytosis with chlorothiazide.

A recent case report (M. B. Chrein and I. L. Rubin, *J. Amer. med. Ass.*, July 7, p. 54) describes a patient who suffered concurrently with two different severe side-effects on hydrochlorothiazide and illustrates the kind of dangers which may be associated with oral diuretic therapy. The patient was a 76-year-old woman who had been on treatment with the drug on a dosage of 50 mg. daily for over six months. She then presented with weakness, raised temperature, and slight cyanosis. When admitted to hospital, a blood count showed white blood cells of only 850 per c.mm. She was also suffering from uraemia, with a blood urea nitrogen of 121.5. This was thought to be due to acidosis caused by the potassium loss which had occurred as a consequence of her diuretic treatment. The treatment adopted was to stop the administration of hydrochlorothiazide and to give intravenous fluid, potassium chloride, and penicillin. The patient gradually improved on this regime. Her white blood cells returned to normal over a period of a few weeks and her blood urea nitrogen declined in the same period.

There seems little doubt that with this patient the cause of the agranulocytosis was hydrochlorothiazide, since all the other drugs which she had been taking before admission were readministered to her in hospital following her recovery without causing a recurrence. The authors, understandably enough, were unwilling to readminister hydrochlorothiazide itself, so that the connexion between drug and toxic effect was to that extent circumstantial. It seems likely enough that hydrochlorothiazide carries a risk of blood dyscrasia similar to that associated with chlorothiazide itself. While reports of

this complication are not common in relation to the very wide use of the benzothiadiazine group of drugs, and the agranulocytosis was in this instance fortunately reversible under treatment, it is a danger to watch out for nevertheless.

Sorbide Nitrate (1,4,3,6-dianhydro-sorbitol dinitrate)

" Vascardin " (Nicholas Laboratories).

Sorbide nitrate is a member of a group of drugs which cause dilatation of the coronary arteries. Other members of this group are amyl nitrite and glyceryl trinitrate, which were first introduced into medicine over 50 years ago. The fact that the duration of action of these earlier drugs is limited has led to the study of other compounds in an effort to overcome this disadvantage. Later developments such as erythrityl tetranitrate and pentaerythritol tetranitrate have been claimed to exert a more protracted vasodilator effect. Sorbide nitrate is a compound of this kind.

It has been demonstrated in animal experiments that sorbide nitrate reduces coronary artery resistance when given intravenously or intraduodenally, but no equivalent to the intermittent arterial contraction found in coronary spasm has been reproduced in animals, so that these laboratory experiments have limited clinical relevance. Studies of its effectiveness in patients with angina pectoris[1] have shown that between half and three-quarters of 51 subjects had an improvement in symptoms. There was some evidence that a fairly long duration of action was obtained in about one-third of the patients. This kind of result from clinical trial is not uncommon with the " long-acting " nitrites. It is questionable how much it really means in terms of clinical advantages. Suggestion is a strong factor in angina, both in its precipitation and in its relief, and precise clinical evaluations are difficult to perform. There is no convincing evidence that sorbide nitrate is an improvement on glyceryl trinitrate (nitroglycerin).

Dosage.—The recommended dosage of sorbide nitrate is one or two tablets twice or three times a day as indicated, as a prophylactic treatment for avoiding anginal attacks. For an acute attack, one tablet can be used sublingually.

Side-effects.—The main side-effect is vascular headache, reported in one series to occur in 14 out of 29 patients.[2] The headache gradually diminished with continued intake of sorbide nitrate, usually disappearing within a week.

REFERENCES

[1] Shapiro, S., *Angiology*, 1961, **12**, 53.
[2] Joseph, L. G., and Mancini, A., ibid., 1961, **12**, 264.

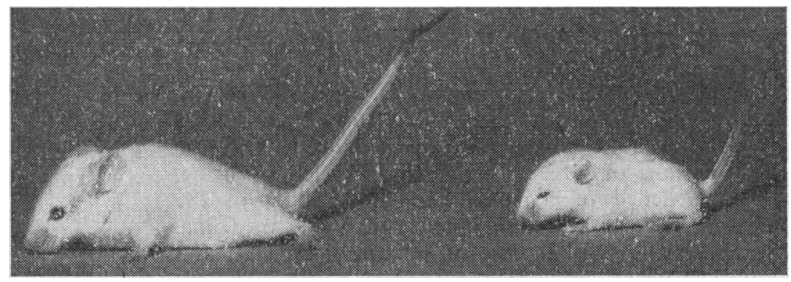
" The A.M.A. has often used events in the British Health Service as propaganda against Government intervention in medical care. In doing so it has nearly always painted a uniformly black picture which being both inaccurate and lacking in analytical profundity has, in my opinion, weakened its case in the United States and has caused much offence in Britain. I hope I shall be able to show from a review of trends in Britain that, although the State has a part to play in medical care, the extent of its intervention should be strictly limited." From an article by Dr. John R. Seale entitled " The British National Health Service." *Northwest Medicine*, 1962, **61**, pp. 448–453.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Thalidomide and the Mouse

SIR,—Nine weeks ago I selected at random 12 mature virgin female mice of the Strong A line from a large colony maintained by brother–sister mating for a number of years. Each female was mated with a full brother. The pairs were placed in cages adjacent to the remainder of the colony and received the same diet. The only difference in regime was that they received a large dose of thalidomide in the form of an aqueous suspension (0.5 g. thalidomide/100 ml. water) in lieu of drinking-water. The experiment is controlled by the presence in the remainder of the colony of numbers of similar breeding pairs. As of now from 12 pairs receiving thalidomide there are 26 living young, whilst 12 control pairs have produced 75 live young. The loss in young in the experimental group is due to a combination of resorption of embryos *in utero* and death of mice in the month after birth. Although the young which have survived in the experimental group show no malformations obvious on external examination they are remarkably stunted, as can be seen by comparison with a typical specimen with a control mouse of the same age (see Fig.). In order to rear enough of these " thalidomide " mice to carry on the experiment through further generations it has proved necessary to stop the administration of the drug for short periods of time.



Female mice of the Strong A line, 40 days old. The animal on the right is from a litter born to parents receiving a suspension of thalidomide in lieu of drinking-water.

It is interesting to note that in experiments in which thalidomide was administered at double strength difficulty in parturition was experienced. In one such case post-mortem of the dam revealed the presence of deformed young; the extent of their deformities is at present under examination.

I report these findings at this early stage as an illustration of the thesis that drugs should be tested for teratogenic activity in the first place on members of a large animal colony where genetic variation is reduced to the minimum and where the life histories and pregnancy data of the whole colony are available as controls. Congenital malformation is but one form of pregnancy wastage, and other forms, resorption and reduction of litters and stunting of young, may be equally valuable in pointing to the need for caution in the introduction of a specific drug.—I am, etc.,

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