The Antagonism of Therapeutic Agents: and what it teaches. The Essay to which was awarded the Fothergillian Gold Medal of the Medical Society of London for 1878. By J. MILNER FOTHERGILL, M.D., Edin., Member of the Royal College of Physicians of London, etc. London: Macmillan and Co., 1878: Pp. 150.

A PRIZE essay is always approached by readers with favourable expectations, and these are intensified if the author has previously produced a well-written book. In the present instance such expectations have not been disappointed. The subject "of the antagonism of therapeutic agents" has been extensively investigated, both experimentally and clinically, during the last few years by a considerable number of very competent men, many reliable observations have been made, and certain practical results achieved; but these are scattered over periodical literature or contained in monographs not generally accessible, so that Dr Fothergill has performed a real and valuable service in presenting, as he terms it, "a fair bird's-eye-view of the whole subject," so far as that can be done at this comparatively early period. He has executed his self-imposed task, we think, with judgment, and has brought an important and interesting field of observation, in a clear and suggestive manner, before the minds of the profession.

The book is divided into seven chapters. The first deals with the subject of experimental inquiry, and occupies thirty-five pages.

Opium and *belladonna*, it would appear, have been suspected to have antagonistic relations to each other since 1570,—the first definite attempt to utilize this antagonism having been made by Horstius in 1661.

The effects of *belladonna* on the pupil of the eye naturally led observers to experiment as to the other actions of drugs which contract the pupil, when given along with it. Hence a valuable series of observations as to the antagonism which exists betwixt *Calabar bean* and *belladonna*. The famous monograph by Professor Thomas R. Fraser is copiously appealed to on that subject. The experimental investigation by the late Professor J. H. Bennett on the antagonistic relations of *chloral hydrate* and *strychnia* is then described at considerable length, as also his subsequent experiments on rabbits with *chloral hydrate* and *Calabar bean*—the inferences drawn being, "(1) that *chloral hydrate* modifies to a great extent the action of a fatal dose of extract of *Calabar bean*, mitigating symptoms and prolonging life; (2) that *chloral hydrate* in some cases saves life from a fatal dose of extract of *Calabar bean*."

Professor Bennett next investigated the antagonism betwixt *morphia* and *atropia*. This inquiry had been previously made the subject of experiments by Dr John Harley in England, and by Weir Mitchell, Keen, and Morehouse in America. All these observers, including Bennett, demonstrated the antagonism generally, and the effects upon the *cerebrum* in particular.

The investigation carried on by Dr Alexander H. Bennett as to the relations of *morphia* to the different vegetable principles *theine*, *caffeine*, *cocaine*, and *guaranine* is next detailed. A subsequent series of experiments were made to test the action of *strychnia* and *Calabar bean* when given simultaneously. It was found that less than the minimum lethal doses of *strychnia* and *Calabar bean* given together cause death. This is what we might expect if they are not antagonistic.

Professor McKendrick conducted a series of experiments to test the antagonism of *bromal hydrate* and *atropia*. The *atropia* seemed to modify the effects of the *bromal hydrate*; but the converse did not hold good; the *bromal hydrate*, when injected, was powerless to avert death after a lethal dose of *atropia*.

The experiments of Dr Crichton Browne on the effects of *picrotoxine*, as modified by chloral hydrate, are next described. They are full of interest, and in some points suggestive practically. He has ascertained incidentally that the effects of *chloral* are more pronounced on animals with convoluted than with smooth brains, and that idiots take larger medicinal doses of *chloral* than other persons, whether sane or insane.

Dr Fothergill's own experiments to illustrate the antagonism of *aconite* and *digitalis* are next described. When *digitaline* and *aconite* were administered to rabbits simultaneously, due attention being paid to the minimum lethal dose of each, previously ascertained, it was found that the action of the *aconite* was little influenced, but if the *digitalis* was given some hours before (five to nine), a distinct protective influence was exercised.

In another investigation, small non-lethal doses of *atropia* following lethal doses of *aconitine* had a striking effect in promoting recovery. It was requisite, however, to give the *atropia* not later than sixteen minutes after the *aconitine*, in order to arrest the lethal action.

The effects of *atropia* on *chloral hydrate* previously administered were discouraging—very inferior to those of *strychnia*, observed by Professor Bennett.

Another experiment was devised to ascertain the effect of lethal doses of *strychnia* on lethal doses of *aconitine*. It seems to be very considerable; but the opposite remains undetermined.

Digitalis exercises no or very little influence over the failure of the respiration induced by *aconite*. Its effect, however, when given some hours before the *aconite*, illustrates how closely the respiration and the circulation are linked together, and how difficult it will be to separate the action on the heart from that on the respiration in trying to differentiate the action of these two poisonous agents.

Professor S. Ringer, observing the opposite action of *atropia* and *jaborandi*, devised the following experiment: He gave $\frac{1}{3}$ of a grain of *pilocarpine*, the principle of *jaborandi*, to a patient subcutaneously; free salivation and sweating were established; he

injected $\frac{1}{100}$ of a grain of *atropia*; in five minutes the skin was quite dry. Two cases of *belladonna* poisoning shortly after enabled him to test the antagonism in the converse manner.

Chap. II. entitled "Practical Inquiry—Action of Drugs chiefly as ascertained by Experiment—Calabar Bean," contains some interesting matter; but, with our limited space, this and the remaining chapters must be dismissed in a very summary manner. Dr Crichton Browne, acting on the suggestive observation of Professor Fraser, that *Calabar bean* lowers both the pulse rate and respiration, and, at the same time, has a depressant action on the spinal motor centres, conceived the idea of administering the drug in the violent outbreaks of excitement to which cases of general paralysis are liable. He found that it calmed the patients, and also deprived them to a great extent of that remarkable muscular force so dangerous both to themselves and their attendants. The drug also seemed to exercise a marked control over the progress of the malady.

It has been suggested by Dr Wood of America, referring to Professor Fraser's experiments, that when *atropia* acts as an antidote to *Calabar bean*, it does so by its stimulant action on the respiratory nerves. *Chloral hydrate*, a hypnotic of great value, should be given with the greatest caution in cases where the circulation and respiration are both involved, such as in chronic bronchitis with right cardiac dilatation, valvular disease, etc., because it not only acts on the circulation, but powerfully affects the respiration. It is indicated, on the other hand, when it is desirable to diminish the energy of the respiration. In poisoning with *strychnia*—if given promptly—Professor Bennett found it very valuable in arresting the tetanic spasm of the muscles of respiration. Macnamara found it very efficacious in traumatic tetanus,—seventeen out of twenty being saved. We see also, how when given empirically in laryngismus stridulus, in asthma and whooping-cough, its beneficial effects may be explained.

Morphia.—"Death," says Wood, "occurs from opium in the great majority of cases by failure of the respiration." We can see, then, that as *belladonna* or *atropia* acts upon the respiratory centres, the antagonism of these drugs becomes readily intelligible. *Morphia* is a dangerous drug in *bronchitis*. It arrests secretion, increasing the difficulty of expectoration and respiration, and has a tendency to paralyze the respiratory centres already embarrassed. It effectually checks the hacking cough of phthisis, but at the same time it lowers the respiration, causes sweating, and impairs the appetite. By adding a little *atropia* to the mixture, Dr Fothergill believes that the sweats are checked, while the *morphia* allays the cough without being interfered with by the *atropia*. Attention to the same principle would lead us to give *belladonna* in asthma, and *ammonia* or *strychnia* in cases where the respiration is failing.

Strychnia.—When death occurs in poisoning by this drug, it is brought about by asphyxia, the muscles of the thorax being spasmodically contracted so as to arrest respiration. Dr Fothergill thinks it a fair induction, that, in smaller doses, it will act as a stimulant to these muscles, not directly, but through the respiratory centres. He gives a very interesting case in illustration of this view, p. 55.

Chap. III. "The Rhythmical Discharging Centres: and Effects of Drugs thereupon."—This contains a brief but interesting statement of the views at present held regarding the nerves which preside over the circulatory and respiratory functions. We have no space for entering into details; but the subject deserves attention.

Chap. IV. "Action of drugs upon the circulation."—As might be expected, the author bestows a good deal of time on his own early investigations respecting *digitalis*. In accordance with them and with later inquiry, the position which the drug now holds is that of a cardiac tonic; it increases the energy of the ventricular contractions. His doctrine is this: *digitalis* excites more perfect ventricular contraction; the arteries are better filled with blood; and consequently the heart itself is better nourished, while the brief diastolic sleep is lengthened. Betwixt the longer rest and the improved nutrition, the heart is enabled to grow and to increase in power. He considers carefully various forms of cardiac disease in which *digitalis* can be used with marked beneficial effect, and others in which only partial results can be anticipated. The following sentence is important: "Many persons who have not carefully studied the mode of action of *digitalis* say: 'it always does good when the bulk of urine is increased; or, it always does good when its diuretic action is established.' Quite true! But this diuretic action is really the evidence of its effect upon the circulation. When it increases the bulk of urine, *digitalis* is producing its effect upon the circulation."

The whole of this chapter will repay an attentive perusal.

Chap. V. "The Respiration."

"There can exist no longer any doubt that we possess in *atropia*, in *strychnia*, in *ammonia*, most powerful means for acting upon the respiratory centres when these are being paralyzed by toxic agents."

Respiratory Depressants.—*Opium* and *chloral*, for example, exercise, as we know, a potent influence over the cerebro-spinal centres generally, and, by arresting their activity, procure sleep; but be it remembered, that they exert a still more pronounced power over the rhythmically discharging centres which preside over the respiration and the circulation—that, in fact, they kill by their effects upon these very centres. We have long known empirically that their use is dangerous and disastrous in cases where the breathing is much oppressed and failing; we now understand, from experimental investigation, how this should be the case. The

life of the individual depending in great measure upon the energy with which forcible respiration is maintained, if these efforts are arrested by a narcotic, he sleeps and may never awake. The risk is increased by the circumstance that these narcotic agents diminish also the activity of the centres in the *medulla*, and reduce thereby even the muscular efforts set up by the rhythmic explosions of the automatically-acting centres.

Respiratory Stimulants.—Without going over ground already traversed, it may be noted, "that where there is dilated heart in chronic bronchitis with emphysema, and *digitalis* gives but imperfect relief, the addition of *strychnia* will usually make it much more effective." "*The effects of temperature* are most important, and must be borne in mind carefully in all attempts to stimulate the respiration and the circulation, by means of agents which act upon the rhythmically discharging centres, which evolve the impulses that maintain the muscular movements necessary to each."

Chap. VI. "Practical Use of the Antagonism of Drugs in actual Poisoning." Some interesting illustrations of the foregoing portion of the essay are given, and merit a careful perusal.

Chap. VII. is essentially a recapitulation of the conclusions previously reached; but one or two suggestive sentences may be quoted.

"In a case of acute bronchitis where the phlegm is loose, the patient bathed in perspiration, and the powers failing, *ammonia* and *strychnia* should be given together in a vehicle, like *squill*, *senega*, or *ammoniacum*."

"In death by chloroform, either the respiration or the circulation fails. Is it possible to obviate this danger by the use of some agent which stimulates the centres connected with these systems, given synchronously?"

We regret the length to which this review has extended; but the inherent importance and interest of the essay must be our apology.

Lectures on Dermatology; delivered in the Royal College of Surgeons of England in 1876-77-78. By ERASMUS WILSON, F.R.S., F.R.C.S., Member of Council, and Professor of Dermatology. London: J. & A. Churchill: 1878.

WE have read this volume with much interest and no little profit, for it is pleasantly written, the type is clear and distinct, and the bulk not unwieldy. The works of the veteran Professor of Dermatology are in themselves worthy of all respectful attention; and all the more, as here new light is shed on many rather obscure subjects. Even when we cannot agree with the opinion expressed, we must own that the suggestions made are ingenious, though to