

ment spasm develops in the apparent absence of any disease.⁷

When the radiographic or gastroscopic appearances are conclusive, laparotomy is preferable to a policy of wait-and-see. But laparotomy also has its limitations: a benign ulcer or early malignant infiltration is not always detectable, and a malignant ulcer may appear benign; an inflammatory mass around the duodenum is not malignant⁸; so sometimes the diagnosis can be established only by microscopic examination.

ADENOSINE AND THE HEART

Drury, in 1936,⁹ described detailed studies of the action of adenosine derivatives on the heart in small animals. The main effect was on the conducting system, a sinus slowing and auriculoventricular block. Green and Stoner⁹ found that these compounds also caused a transient fall in blood-pressure. Honey et al.¹⁰ showed that adenosine could produce heart-block in healthy man. The effect of magnesium adenosine triphosphate on the electrocardiogram (E.C.G.) was extensively studied by Wayne, Goodwin, and Stoner¹¹ in patients who were receiving intravenous injections of this substance as treatment for rheumatoid arthritis. When the injection was made rapidly there was invariably subjective disturbance, consisting of hyperpnœa, cough, flushing, and transient sensation of faintness. In all cases the blood-pressure fell, the greatest reduction being by 100 mm. Hg. Changes in the E.C.G. were remarkably constant. All doses (5-15 mg.) produced brief sinus bradycardia followed by sinus tachycardia. Larger doses (15-30 mg.) produced pronounced sinus slowing, and in addition depressed the conducting tissues with consequent first and second degree auriculoventricular block, Wenckebach blocks, and occasionally complete asystole for several seconds. The action of adenosine was similar to that of adenosine triphosphate but less distinct. The production of auriculoventricular block by adenosine triphosphate was prevented by atropine, indicating that this action is mediated through the vagus. Adrenaline produced a similar effect to atropine. The action of adenosine triphosphate on the heart was not confined to the conducting tissues; alteration in the ST segment and ventricular ectopic contractions suggested a direct effect on the myocardium. These myocardial effects were found to be decreased by the magnesium ion, which potentiated its depressant action on the conducting system.

Adenosine triphosphate also brings about dilatation of coronary arteries in animals,¹² and various forms of adenosine have been used from time to time in the treatment of cardiac and peripheral vascular disease. Wayne, Goodwin, and Stoner¹¹ considered that use of this substance for such purposes might be unwise in view of the direct effects on the myocardium; while Honey et al.¹⁰ did not regard adenosine as useful for the treatment of heart-disease. In a letter on p. 1125 Somló describes the treatment of supraventricular paroxysmal tachycardia by rapid intravenous injection of adenosine triphosphate 20 mg. Both the subjective effects and the E.C.G. changes were essentially similar to those described previously, except that there was invariably ventricular asystole, sometimes followed by bifocal ventricular ectopic beats which in turn were followed by normal beats and then by normal sinus rhythm. There were no untoward side-effects.

Adenosine triphosphate may prove a powerful therapeutic weapon against paroxysmal tachycardia. But it should be remembered that supraventricular tachycardia

is often a benign condition which is a nuisance rather than a danger, and that attacks commonly terminate spontaneously. Most physicians, therefore, prefer first to try simple measures, such as carotid pressure or "trick" manoeuvres to induce vagal stimulation, sedation, or oral administration of digitalis. But not all cases respond to such treatment; and long-continued paroxysmal tachycardia may constitute a real danger to the patient. In such circumstances adenosine triphosphate might certainly be considered; and this drug may be more effective than others, such as methacholine chloride, quinidine, or procainamide, which are not uncommonly used. Adenosine triphosphate might with advantage be given as the magnesium salt, which has less direct action on the myocardium.¹¹ In view of its action on the myocardium, great caution is necessary in administering it to patients with organic heart-disease and much cardiac enlargement; but need to terminate the ectopic rhythm may justify the risks. Adenosine triphosphate should not be given without E.C.G. control, and preferably atropine should be at hand in case prolonged asystole ensues. It seems possible from Somló's observations that adenosine triphosphate might induce ventricular tachycardia, but this has apparently not arisen on any of over four hundred occasions, referred to by Dr. Somló, when the drug was administered to terminate a supraventricular paroxysm of tachycardia.

Somló considers that the response of supraventricular tachycardia to adenosine triphosphate is so specific as to constitute a diagnostic criterion. But of course, as he would no doubt agree, the diagnosis should be established clinically and electrocardiographically before the drug is administered.

A SNOW CENTENARY

EPIDEMIOLOGISTS have been accused of having a Broad Street Pump fixation which blinds them to the needs and opportunities of work on diseases of more immediate importance than cholera. Quite unabashed, the section of epidemiology and preventive medicine of the Royal Society of Medicine met on May 17 at the London School of Hygiene and Tropical Medicine to celebrate the centenary of the publication of Dr. John Snow's classic *On the Mode of Communication of Cholera*. A group of students working for the diploma in public health had prepared an exhibition (which will be open for a month) of Snow miscellanea ranging from a hitherto little-known portrait painted at the request of Queen Victoria to an account of the findings at necropsy after his tragically premature death from chronic renal disease at the age of forty-five. The exhibits outline the main facts of his life and the steps which led him to record his belief that cholera was spread through infection of the community's drinking-water by the patients' dejecta, first rather tentatively in 1849, and then with forceful conviction in the more substantial edition of 1855. This book, which as Wade Hampton Frost said in his introduction to the Commonwealth Fund reissue "should be read once as a story of exploration and many times as a lesson in epidemiology," is indeed the exemplar of the epidemiological method at its best.

Prof. A. Bradford Hill, F.R.S., the section's president, pointed out that Snow had to wait for confirmation of his thesis until the disastrous epidemics of the 1850s, when the removal of the intake of water supplied by the Lambeth Company up the Thames to Ditton produced the remarkable contrast in cholera mortality which formed the basis of Snow's "experiment on the grandest scale." In Southern London the pipes of both the Lambeth Company and the Southwark and Vauxhall Company (which drew "the filthiest stuff ever drunk by a civilised community" from the Thames in the heart of the city) went down every street supplying rich and poor, clean and dirty, in a manner which had all the

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appearances of random allocation. Yet, as Snow found out by arduous "shoe-leather epidemiology," the absolute number of deaths in the houses supplied by the Southwark and Vauxhall Company was vastly greater than among the customers of the other. Unfortunately, he did not then know the number of houses supplied by each company in the area, and could not give his dramatic contrast the rigorous basis which only comparable rates provide, until a year after the publication of this main work. Meanwhile, the epidemic centred round the pump in what is now Broadwick Street had exploded with appalling results. Within three days over three hundred people were dead from cholera. The dramatic account of Snow's discovery of the focal importance of the pump and his appearance before the local vestry to recommend the removal of the pump-handle is well known. But Snow himself shunned the facile argument that the epidemic was thereby halted, and indeed he pointed out that the panic-stricken flight of the inhabitants had already done that by what would now be called "the exhaustion of susceptibles."

The removal of the pump-handle was thus symbolic rather than effective, signalling the beginning of the end of cholera as an epidemic disease in this country. That that end was not at once achieved is a sad reflection on the scientific and moral climate of the times. For, as a contribution from Prof. James Mackintosh reminded the meeting, much of England's prosperity in the reign of Queen Victoria was illusory and its morality superficial. The local vestry dealing with the Broad Street epidemic was rebuffed by Sir Benjamin Hall; and for years after the outbreak Lankester, Snow's helper and friend, protested forcibly against the failure to close the surface-water pumps in the district. Snow's views were attacked in the *Times* by the secretary of the Private Enterprise Association, whose disinterestedness was clearly suspect; but even within the profession his ideas received little encouragement. Men of manifest good will, such as Simon, were so overwhelmed by Chadwick's *Report on the Sanitary Condition of the Labouring Population* that they were unable to conceive of a specific agent of disease other than the vague miasmata rising from filthy environment. With shame we acknowledge that *The Lancet* accused Snow of riding a scientific hobby-horse by insisting on the paramount dangers of the sewer. Despite his solitary abstemious habits and his lack of eloquence, Snow, by the weight of his circumstantial evidence, eventually had his views generally accepted. So today we join in honouring the work of a man who rid his country of cholera, not by technical innovation, but by courageous application, acute observation, and an inspired and logical arithmetic.

HEAD INJURIES IN AMATEUR BOXING

It has been estimated¹ that after five years' fighting as many as 60% of professional boxers have detectable mental changes, and that 5% have the slow dementia, rigidity, and tremor of punch-drunkenness. Less is known about the risk to our 100,000 amateur boxers²⁻⁴; but obviously this is not so great.

Electro-encephalographic (E.E.G.) changes in boxers have been extensively studied. Dow et al.⁵ found that such changes tended to disappear thirty minutes after the injury; but Busse and Silverman⁶ reported persistent abnormalities in over a third of 24 professional boxers, compared with Gibbs's⁷ figure of 15% for controls. The degree of E.E.G. abnormality could not be correlated with

the length of the boxing career, but the more serious disturbances are found in men who have been knocked out and in the less efficient fighters. Larsson and associates³ studied 75 amateur boxers, of whom 44 were examined both before and after their bouts, and remaining 31 only because they were suspected of having sustained head injuries. An E.E.G. record was taken within thirty minutes of the match. In the first group 1 in 8 of apparently uninjured boxers had E.E.G. abnormalities—a proportion close to that found from records taken before the fights—but after knockdowns and knockouts the abnormality-rate rose to about 1 in 3. Of the 31 boxers suspected of having sustained head injuries over half showed E.E.G. abnormalities. Control studies excluded effects on the E.E.G. of physical exertion and it seems probable that, in the first group, records before the fights eliminated confusion due to maturation defects.

As Blonstein and Clarke² point out, ideally every boxer should undergo E.E.G. examination before taking part in boxing. By comparison of the initial record with subsequent records the clinical significance of E.E.G. changes might be made clearer. Meanwhile the risks to amateur boxers of repeated minor cerebral damage cannot be accurately assessed; but it seems most unlikely that these ever amount to the severe disorders sometimes found in professional boxers.

MECHANISM OF FEVER

The body-temperature remains constant by a balance between heat production and heat loss. Except for slight diurnal variations and the ovulatory changes in women, the temperature in health is remarkably constant. We are almost entirely ignorant of the mechanism by which the body-temperature is increased in disease, of the metabolic effects of pyrexia, and whether pyrexia is advantageous to the organism.⁸

Some stages in the febrile response have been investigated experimentally. The administration of a pyrogenic substance is followed by a latent period, varying between species but constant for a given species; in animals it lasts for 15-30 minutes, and in man for 45-90 minutes. During this interval there is a leucopenia,⁹ and a sequestration of leucocytes in small blood-vessels. Wood¹⁰ has suggested that during this sequestration leucocytes release a pyrogenic substance, which, according to Farr et al.,¹¹ combines with a factor contained in the serum, α or β globulin in the serum. It is not known whether this factor or other factors exert their effects, but they act directly on the thermoregulating centres.

The suppression of pyrexia by cortisone¹⁴ has been studied by Atkins et al.,¹⁵ who induced fever in man by administering either pyromen or native diphtheria toxin. They found that such suppression was independent of the initial leucopenia, and the "serum factor" was unaffected. They concluded that cortisone must produce its antipyretic effect by acting on some "later and as yet undefined" stage of the fever mechanism.

As Atkins et al. remark, artificially induced fever involves mechanisms other than those which operate in the natural man. Long¹⁶ has shown that whereas man, monkey, and guinea-pigs react similarly to cortisone, rats, mice, and ferrets react differently. In evaluating the effect of cortisone, differences between species may be of utmost importance. Finally, it could be equally well argued that cortisone was producing its antipyretic effect in rabbits by interfering with the liberation from the blood of the postulated initial pyretic substance.

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