

## PREVENTING RECURRENCES OF RHEUMATIC FEVER

The incidence of acute rheumatic fever is declining, partly, perhaps, because of improved nutrition and better social conditions, partly because of the wise and prevalent practice of treating streptococcal tonsillitis with an antibiotic, and partly for unknown reasons, but acute rheumatic fever still occurs, and still causes serious permanent crippling heart disease. Although we cannot say exactly how much damage a recurrence of rheumatic fever does to an already damaged heart, it is clearly desirable to prevent recurrences if we can. If there is no evidence of carditis after an attack of rheumatic fever, it is equally or even more desirable to prevent damage by another attack. The best drug to give is penicillin.<sup>1</sup>

The usual form of penicillin used for prophylaxis consists of tablets of penicillin G, one tablet of 200,000 units given twice a day. This costs about 2s. 2d. a week, but the value of the prevention of rheumatic fever can hardly be expressed in terms of cash. There are two difficulties. The tablets deteriorate unless they are kept in an airtight tin, and not all patients can be relied on to take them. As a result various workers have advocated a single intramuscular injection of 1,200,000 units of benzathine penicillin G each month. Injections, however, are not popular with children, and there is a higher incidence of allergic reactions than with oral penicillin. Chancey and colleagues<sup>2</sup> found a reaction rate of 5.2% with intramuscular benzathine penicillin G, as compared with 1.1% with the oral method.

The duration of continuous prophylaxis to be aimed at is a matter of opinion. The American Heart Association<sup>3</sup> recommended "continuous prophylactic penicillin throughout life, or until new knowledge makes this recommendation invalid." The Royal College of Physicians Committee<sup>4</sup> recommended that it should be given "for five years, or till leaving school, whichever is the longer"; Bywaters and Thomas agree with this advice.

While the usual relapse rate found with continuous prophylactic penicillin is about 4%, the rate without such treatment is likely to be anything from 40 to 70%. In this connexion a recent paper by R. A. N. Hitchens<sup>5</sup> contains much interesting information. Hitchens describes the incidence of recurrences of rheumatic fever in 470 Cardiff schoolchildren attending a school rheumatic clinic. They had all

had rheumatic fever with carditis, and came under observation between 1931 and 1950, before penicillin prophylaxis was used. Recurrent episodes occurred in about a third during the period of observation. There were recurrences in 47% of those under supervision from the onset of rheumatic fever to school-leaving age, and in 54% of those who were observed continuously for three years or more after the onset. Hitchens found a significant incidence of recurrences in the summer months, indicating that penicillin must be given summer and winter. An important finding was that there was a risk of the first recurrence as long as seven years after the initial attack; the risk diminished only slightly after the first four years. Among children observed from the onset to school-leaving age, cardiac abnormalities were found at the end of the period of observation in 74% of those who had recurrences and 61% of those who did not. It would be interesting to know the corresponding incidence of carditis in those who initially had no evidence of carditis and who had penicillin prophylaxis, and the incidence in a similar group who had no penicillin, but we have no information on this point. Hitchens's paper supplies further good evidence that when a child has had rheumatic fever continuous penicillin prophylaxis should be given for many years to prevent recurrences.

## TOBACCO SMOKING AND RESPIRATORY DISEASE

The evidence that tobacco causes disease of the respiratory tract is now based on many different types of study—clinical, chemical, pathological, statistical. Doctors have long known that smoking predisposes to "chestiness," and on clinical grounds suspected that it might be a cause of lung cancer before the statisticians came along with their compelling data. Fresh evidence continues to appear from a wide variety of studies that tobacco plays some part in the aetiology both of inflammatory and of malignant disease. In our opening pages this week Professor E. L. Wynder, of New York, reviews many of the experimental attempts made to discover carcinogenic substances in tobacco tar and smoke. These are still in the early stages; though they show that substances carcinogenic to mice occur as products of burnt tobacco, much work has yet to be done to define their action in man. An important practical consequence of such laboratory researches could be the modification of tobacco, or of the way it is smoked, so that it becomes less harmful. Professor Wynder believes that though reduction of the tar content of cigarettes by manufacturers—a trend he has observed in the U.S.A.—will not prevent a smoker from developing lung cancer, "present evidence indicates that it will reduce his chances of developing this disease."

<sup>1</sup> Bywaters, E. G. L., and Thomas, G. T., *Brit. med. J.*, 1958, 2, 350.

<sup>2</sup> Chancey R. L., Morris, A. J., Conner, R. H., Catanzaro, F. J., Chamovitz, R., and Rammelkamp, C. H., *Amer. J. med. Sci.*, 1955, 229, 165.

<sup>3</sup> American Heart Association, *Circulation*, 1955, 11, 317.

<sup>4</sup> Royal College of Physicians, *Rheumatic Fever Committee*, 1957, London.

<sup>5</sup> Hitchens, R. A. N., *Ann. rheum. Dis.*, 1958, 17, 293.

<sup>1</sup> Hammond, E. C., *Brit. med. J.*, 1958, 2, 649.

The usefulness of a filter in this connexion depends on its capacity to lower the total tar content of the smoke.

The tobacco itself also acts as a filter, whose effectiveness diminishes as the tobacco burns away. This fact has been suggested as a possible explanation of why lung cancer is less prevalent in the U.S.A. than in Great Britain, though the average consumption of cigarettes in the two countries is much the same. This week Dr. R. Doll and Professor Bradford Hill throw some light on the problem with the help of colleagues in the Social Survey Division of the Central Office of Information. The Social Survey collected the butts of smoked cigarettes from a sample of men and women in England and Wales. In all 71 smokers sent in 772 butts, and the average length of them was 18.7 mm. This is compared with an average length of 30.9 mm. of butts collected in the American investigation reported recently in this *Journal* by Dr. E. Cuyler Hammond.<sup>1</sup> Clearly if these figures are representative of cigarette butts in the two countries, and have been for perhaps twenty years, they suggest that Britons have indeed been breathing larger quantities of carcinogenic material and that this might account for the higher incidence of lung cancer.

One of the difficulties of investigating the relationship between smoking and disease is the large number of other variables which interfere with respiratory physiology—for example, age, air pollution, weather, infections, and predisposition to bronchospasm. Some of these may change from day to day, or even from hour to hour. A typical day in the life of a smoker with respiratory symptoms may start with a quarter of an hour of wheezing and hawking. Then, provided there is no fog, he is comparatively free of symptoms until the early evening, when his symptoms return, particularly if he slumps in an armchair. During the night he may wake with paroxysms of coughing. His chest may be completely clear during the summer months. If reliable conclusions on the effect of smoking are to be drawn from tests of physiological function, selected subjects must be very carefully studied and be sufficiently numerous to offset statistical errors. Ideally, the tests should cover lung volumes, mixing efficiency, ventilation, and diffusing capacity under standard conditions, but this would be practicable only in a small sample. As a compromise, a simple test of ventilatory capacity might be adopted, which would be intended to measure the degree of obstruction to air-flow produced by tobacco smoke, principally in terms of excessive mucus, mucosal oedema, and bronchospasm. Two such tests are at present undergoing extensive trials; both are easily and quickly performed and are applicable to large surveys. In one, the maximal mid-expiratory flow rate is recorded by breathing out fast through a portable flow-meter. The other method, used by Dr. I. T. T. Higgins in his studies reported at p. 325 of the *Journal* this week, takes into account the maximum volume of air which can be expired forcibly in three-quarters of a second, using a spirometer with an electronic timer. The mean of three readings is multiplied by 40 and is expressed as the indirect maximum breathing capacity. The test is

reliable, as has been repeatedly observed, and when applied to large series of smokers and non-smokers was found by Higgins to reveal an estimated reduction of 9 litres per minute, or about 10%, in the smokers. Curiously, no significant downward trend with increasing tobacco consumption could be detected. These studies, in conjunction with those that Higgins refers to, show that tobacco smoking interferes with pulmonary ventilation.

### SKIING AND THE ADRENALS

At this time of year, when many people travel abroad in search of sun and snow, medical journals are apt to draw attention to the hazards of winter sports.<sup>1</sup> By no means all the returning sportsmen, however, are encased in plaster, and many are only too eager to testify to the invigorating effects of the holiday. Those who are physiologically inclined will be especially interested in the hypothesis advanced by Dr. L. G. C. E. Pugh at p. 342 that skiing acts as a beneficial stimulant to the adrenal cortex. He took the opportunity, during a skiing holiday, of measuring the eosinophils in three subjects before and at the end of the day's exertions. There was always an eosinopenia after exercise, and in general this was most marked after long periods of skiing. The response tended to fall off as the subject became fit, and a similar effect was noted when one of the subjects performed a series of eight-mile runs. Pugh compares these results with a previous study on Channel swimmers, in whom he found a virtual disappearance of eosinophils accompanied by a great increase in urinary corticoid excretion. By contrast, short bouts of exertion, even to the point of exhaustion, had very little effect on the eosinophil count.

Besides its purely topical interest, this study may provide an answer to some of the apparent paradoxes of adrenal function discussed not long ago in these columns.<sup>2</sup> While it is agreed that the stresses of strong emotion and major trauma are associated with increased adrenocortical activity, it has not been possible to demonstrate a similar response even after severe exertion. The well-known studies of G. W. Thorn and his group<sup>3</sup> on the Harvard boat crew, in which cox and coach had the same increase in adrenal activity as the oarsmen, merely underlined the importance of emotional factors. But even when these were excluded, as in troops on a 15-mile route march,<sup>4</sup> there was no rise in urinary corticoid excretion. Pugh's results show that duration of exercise and fitness of the subject must be taken into account. A short bout of intense physical activity in an unfit individual is no more of a stimulus than a cross-country run in a trained athlete. Conditions must be carefully chosen, and it is likely that the success of the present experiment is due in part to the additional stressor effects of cold, hypoxia, and altitude. There may indeed be a link here with the finding of P. C. B. MacKinnon and her colleagues<sup>5</sup> of decreased palmar

<sup>1</sup> See annotation. *Brit. med. J.*, 1959, 1, 159.

<sup>2</sup> *Brit. med. J.*, 1958, 2, 496.

<sup>3</sup> Hill, S. R., et al., *Arch. intern. Med.*, 1956, 97, 259.

<sup>4</sup> Connell, A. M., et al., *Acta Endocrinol.*, 1958, 27, 179.

<sup>5</sup> MacKinnon, Pamela C. B., MacKinnon, I. L., and Williams, E. S., *Brit. med. J.*, 1959, 1, 199.

sweating, tentatively attributed to adrenal overactivity, at high altitudes. It should be possible to study these various factors under laboratory conditions, especially the influence of training on adrenal activity. Is this, for example, related in any way to the process of acclimatization? If such work is undertaken it would be as well to use biochemical methods for measuring adrenocortical function, since the eosinophil response may not be a sufficiently specific index.

### ARCTIC ANAEMIA

Climate and temperature are not usually considered to be factors that influence the blood count. But R. W. Christie<sup>1</sup> has reported that anaemia occurred in all six members of an expedition engaged on scientific work on the central Ice Cap of Greenland. The drop in blood values was quite large; the average red-cell count fell to 3,700,000 per c.mm. in the second week and the haemoglobin level to 10.8 g. per 100 ml.; the mean corpuscular haemoglobin fell to a minimum of 23.2  $\mu\mu\text{g.}$ , compared with the normal range of 27.3  $\mu\mu\text{g.}$  On the Greenland Ice Cap the altitude varied from 1,000 to 3,600 metres, but this would be expected to increase red cells and haemoglobin rather than cause a fall. The members of the expedition were living under field conditions in spring climates. The temperature varied from 1° to 62° F. below freezing point (-1 to -35° C.); all sorts of weather were encountered; their shelters were unheated but food was ample and good—fresh-frozen meat, dehydrated vegetables, and citrus-fruit juices fortified with ascorbic acid. Clothing was fully appropriate. The difference in this expedition's work was that it required much digging. In order to study the ice, pits were dug from which 11 cubic yards (8 cu.m) of snow and ice were excavated, and these pits were dug every second day for a hundred days. "As might have been expected," says Dr. Christie, "some expedition members were more active than others, and, generally speaking, the most active member had the lowest hematologic values and the least active member the highest." The haemoglobin was estimated by a Sahli haemoglobinometer and its readings were later checked against a standard instrument; red-cell counts were carried out on the spot—and fresh solutions were supplied by parachute drop. A few blood smears were made, and the picture appears to be that of a normochromic microcytic anaemia.

The explanation of this anaemia is not likely to be simple. The only way climate could be expected to influence the figures would be in causing changes in plasma volume; but most of the few reports indicate a contraction of plasma volume, which would cause a relative rise in the red cells and haemoglobin. Previous observations on men under Arctic conditions are few and seem to relate a drop in haemoglobin to exercise. A. Hoygaard<sup>2</sup> studied East Greenland Eskimos, and

O. Wilson<sup>3</sup> the members of an Antarctic expedition; both concluded that haemoglobin levels are lowest in the summer when their subjects were most active and highest in the winter when the climate makes confinement inevitable and physical activity is at a minimum. Experimental evidence has shown that strenuous exercise can produce anaemia, and the Finnish authors M. J. Karvonen and M. Kunnas<sup>4</sup> showed that the red-cell count may fall with strenuous exercise. Christie concludes that the strenuous exercise was the main cause of the anaemia in the members of his expedition and suggests two possible mechanisms: a random destruction from excessive mechanical trauma to red cells, and anoxia of capillary walls leading to diapedesis of red cells and loss into the tissues. The mystery is why the bone marrow is so sluggish in compensating for the lower red-cell count.

This anaemia, then, seems to be a variety of exertion anaemia. Life in the Arctic or Antarctic climate entails so much work in travelling and in keeping alive that the added exertion of the scientific activities is much more of a burden than it would be in temperate climates. But it is worth noting that after two weeks the subjects seemed to be getting used to their changed mode of life and blood values were returning towards normal.

### BRONCHIAL SENSITIVITY TO POLLEN

Charles Harrison Blackley<sup>1</sup> (1820–1900), a Manchester practitioner, deserves to be remembered for his pioneer experimental observations on hay-fever, a disease from which he suffered severely. Using himself as a guinea-pig, he carried out all sorts of experiments, inhaling through his nose or mouth different forms of pollen. By means of kites he calculated the number of pollen granules in the air at various heights, and on one occasion he lived in a hut in the midst of hayfields, remaining immune to pollen so long as the air was filtered. He found that whenever he inhaled pollen through his mouth asthmatic symptoms were produced, but this did not occur when he inhaled nasally. On one occasion, while he was examining some catkin pollen under the microscope, he accidentally inhaled a considerable quantity before he realized the catkins had thrown off so much. The description of his subsequent symptoms makes interesting reading. It was two days before he was fit for duty.

Nearly a century later K. M. Citron<sup>2</sup> and his colleagues have described a technique for measuring bronchial sensitivity by making patients suffering from pollen asthma inhale mixed grass pollen and measuring the effects of the forced expiratory volume before and after. The results are interesting, though the test is not without discomfort and even danger to the patient; adrenaline, aminophylline, and oxygen had to be readily available. Patients were not allowed to leave until they had fully recovered, and they were given a supply of isoprenaline tablets to take away with them. The test

<sup>1</sup> Christie, R. W., *New Engl. J. Med.*, 1958, **259**, 605.

<sup>2</sup> Hoygaard, A., *Skr. norske Vidensk.-Akad., I. Mat.-nat. Kl.*, 1940, **9**, 1.

<sup>3</sup> Wilson, O., *Brit. med. J.*, 1953, **2**, 1425.

<sup>4</sup> Karvonen, M. J., and Kunnas, M., *Ann. Med. exp. Fenn.*, 1952, **30**, 180.

<sup>1</sup> Blackley, C. H., *Experimental Researches on the Causes and Nature of Catarrhus Aestivus (Hay Fever and Hay Asthma)*, 1873, London.

<sup>2</sup> Citron, K. M., Frankland, A. F., and Sinclair, J. D., *Thorax*, 1958, **13**, 229.

was found to be reliable in eliciting specific bronchial reactions in asthmatics whose asthma was due to grass pollen, and did not produce reactions in patients whose asthma was due to other causes. Bronchial sensitivity did not correlate quantitatively with skin sensitivity, nor did skin sensitivity correlate quantitatively with the clinical manifestations of pollen asthma.

Thirteen patients whose bronchi reacted to inhalations of pollen were hyposensitized, and twelve showed a fall in the bronchial response to a second test. In the subsequent pollen season all thirteen did well. Nine were completely free of asthma and four were considerably improved. Five patients not hyposensitized had the usual asthma in the subsequent season. A fall in the bronchial sensitivity was usually correlated with successful hyposensitization.

### THE THYROID IN THE INFANT

The thyroid develops from an outgrowth of the ventral aspect of the anterior end of the foregut. This process grows into the neck and at its tip small solid masses of cells proliferate rapidly. By the end of the fourth month *in utero* the total number of acini of the primitive thyroid are said to have been produced. From this time on the growth of the thyroid is apparently due only to the increase in size of the original acini. Judged by the ability to concentrate radioactive iodine, the cells of the thyroid are functioning from within the first quarter of gestation.<sup>1</sup> Colloid collects particularly in the peripheral acini, and is normally present at birth.<sup>2</sup>

The original outgrowth from the foregut—the thyroglossal duct—is represented in the mature person at its upper end by the foramen caecum at the centre of the tongue, and the track of the duct runs down through the centre of the hyoid bone, and thence by way of the pyramidal lobes of the thyroid to the thyroid isthmus. Remnants of the thyroid or of the duct are thus to be found only at the base of the tongue, or in the midline beneath the chin above the trachea. At birth the thyroid is essentially in its adult relationship to the trachea and the thyroid cartilage, and usually weighs between 1 and 3 g., which, relatively to total body weight, is almost twice the size that it is in the adult.

The relative shortness of the infant neck and the shape of the thoracic inlet make the thyroid appear more lowly situated in the neck than in the older child and adult. This is particularly important when a tracheotomy is performed. The thymus, most of which is in the mediastinum, has upper prolongation to the thyroid isthmus, and lateral prolongations of the thymus occasionally cover the lateral lobes of the thyroid and will obliterate its outline to the palpating finger. In the older child the thyroid cartilage is firmer and more easily palpable and from it the location of the thyroid can be ascertained.

There has been much discussion on aberrant thyroids in relation to thyroid tumours. Such thyroids have

been located in the trachea and in the mediastinum, though, compared with other organs such as thymus or pancreas, the thyroid seems remarkably constant. In a series of approximately 3,000 necropsies on children one aberrant thyroid was seen, and that lingual; and in a series of approximately the same number of sections of thymus from the upper mediastinum no fragments of thyroid tissue were detected. The thyroid, on the other hand, at this age so frequently contains small masses of thymic tissue that this may be counted a normal constituent.

Disorders of the thyroid in infancy were well reviewed by D. Hubble in this *Journal* in 1956<sup>3</sup>, and he pointed out, as have others, that the thyroid is more sensitive to radioactivity than was first thought. Carcinoma of thyroid following irradiation of the thymus has been recognized for a number of years<sup>4</sup>; now there has been a recent report by G. M. Wilson and his colleagues<sup>5</sup> of malignant change in the underlying thyroid following radium treatment of cutaneous naevi of the neck. It is possible that radioactive iodine of very short half-life might be suitable for investigating the location and activity of thyroid tissue. However, autoradiograms of thyroid following the injection of radioactive substances show that the iodine is not universally distributed but tends to be concentrated in small areas, and this makes it doubtful whether iodine tracer studies should be carried out at all in infancy.

### MEASLES EPIDEMIC

In the first three weeks of this year about 41,000 cases of measles were recorded in England and Wales. This is well above the corresponding figures of the last two years—namely, about 9,000 in 1958 and 28,000 in 1957—though, as the graph on p. 382 shows, it is below the highest levels reached in the last nine years. To give some idea of the main features of the disease as it appears to-day and of how it is best treated, we invited some general practitioners to write short reports on the cases they have seen in their practices recently. These appear at p. 380. It is interesting to note, first, that the distribution of the disease is rather patchy at present. It has not yet reached the areas where two of these doctors practise (in South Scotland and Cornwall), and other areas are known to be free of the disease so far. On the other hand, in Kent it is reported to have arrived in time to put the children to bed over Christmas. These writers agree that measles is nowadays normally a mild infection, and they rarely have occasion to give prophylactic gamma globulin. As to the treatment of the disease and its complications, the emphasis naturally varies from one practice to another. Amount of bed-rest, when to administer a sulphonamide or antibiotic, the use of analgesics and linctuses—all these may still be debatable problems in the treatment of what is said to be the commonest disease in the world. But there is probably much in the opinion which one of the writers expresses: "It is the frequent visiting by the interested clinician and not the therapy which produces the good results."

<sup>1</sup> Chapman, E. M., Corner, G. W., Robinson, D., and Evans, R. D., *J. clin. Endocr.*, 1948, 8, 717.

<sup>2</sup> Sclare, G., *Scot. med. J.*, 1956, 1, 251.

<sup>3</sup> Hubble, D., *Brit. med. J.*, 1956, 1, 875.

<sup>4</sup> Simpson, C. L., and Hempelmann, L. H., *Cancer (Philad.)*, 1957, 10, 42.

<sup>5</sup> Wilson, G. M., et al., *Brit. med. J.*, 1958, 2, 929.