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THE SYMPATHETIC TRANSMITTER

The account of the hormones of the sympathetic nervous system and the adrenal medulla in the opening pages of this week's *Journal* is of particular interest, because it is written by Professor U. S. von Euler, whose work in the period 1944–6 did much to focus attention on the substance *nor*adrenaline. In structure *nor*adrenaline is similar to adrenaline except that the nitrogen of the amine group which terminates the side chain is not methylated, and, in German, it is "N ohne radikal." Professor von Euler demonstrated the presence and estimated the amount of an adrenaline-like substance in many organs and nervous tissues, and showed that the compound had the properties of *nor*adrenaline. The amounts were greatest in sympathetic nerves; thus the thoracic and lumbar sympathetic chain and the splenic periarterial nerves contained as much as 30–100 μg. per g. He inferred that *nor*adrenaline is the physiological transmitter of adrenergic nerve action, and supported this inference by the observation that after the nerves have been cut and have degenerated *nor*adrenaline almost entirely disappeared from the organs supplied.

The spleen has been found to contain, per gramme of tissue, about 25% of the amount of *nor*adrenaline in splenic nerves. But the nerves within the spleen do not constitute a quarter of the spleen tissue; hence it seems as if there must normally be a transport of *nor*adrenaline down the nerves into the spleen, in which it presumably exerts some function hitherto undescribed. The sympathetic transmitter is not entirely *nor*adrenaline, but appears to be a mixture of *nor*adrenaline with a small amount (perhaps 5%) of adrenaline. There is considerable difficulty in estimating mixtures of this kind when the amounts available are small, and it is right to pay tribute to the painstaking work which has been done on this subject in the pharmacological department in Edinburgh. So far as is known at present there is little evidence of excess of *nor*adrenaline in the blood in clinical conditions except when there is a tumour of the adrenal medulla. These tumours contain mainly, and sometimes almost entirely, *nor*adrenaline, and they give rise to a large excretion of this substance in the urine—so much that the urine causes a rise of blood pressure when it is injected without treatment into an anaesthetized cat. Therefore to diagnose an adrenal medullary tumour it is better to examine the urine rather than the blood. Von Euler and Engel have shown that when a tumour is present the normal excretion of 30 μg. of L-*nor*adrenaline and of 10 μg. L-adrenaline per day rises to more than 1 mg.

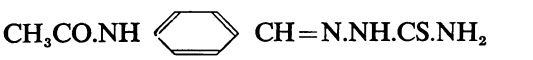
Professor von Euler discusses many of the interesting differences in the physiological properties of *nor*adrenaline and adrenaline. When given to man in amount which causes a large rise of blood pressure, *nor*adrenaline does not cause the anxiety, discomfort, and irritation which are caused by adrenaline. Moreover, Goldenberg and his colleagues have found that there is an important difference in the effect of the two substances on oxygen consumption in man. When infused intravenously at the rate of 0.15 μg. per kg. of body weight per minute, *nor*adrenaline did not affect oxygen consumption, whereas when adrenaline was infused in the same amount the oxygen consumption was increased by 25%. It is clear that there are still important gaps to be filled in our knowledge before a correct estimate can be formed of the physiological roles of the two substances. When the physiology is clearer the part they play in pathological conditions will also be more evident.

THIACETAZONE

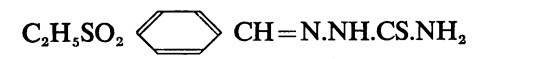
The last five years have seen the intensive study of five chemotherapeutic remedies for the treatment of tuberculous infections. Calciferol (vitamin D_2) has a curative action only in tuberculous lesions of the skin, and its use in pulmonary tuberculosis seems to be definitely contraindicated. The sulphones have proved disappointing in tuberculosis, but in the other great infection caused by an acid-fast bacillus, leprosy, they are undoubtedly of very great value, especially the parent substance 4 : 4′-diaminodiphenylsulphone. Streptomycin has been studied more intensively than any of the other drugs. Its action, although most remarkable in miliary and meningitic infections, is now known to be bacteriostatic rather than bactericidal, and some well-known disadvantages undoubtedly attend its use. Tubercle bacilli resistant to streptomycin have been recovered in the U.S.A., in France, and in Great Britain from patients who have never themselves received the drug. P.A.S. (*p*-aminosalicylic acid), though less active than streptomycin, is also less toxic, and there is now growing evidence to show that treatment with streptomycin and P.A.S. in combination retards the appearance of strains resistant to streptomycin.[1] Of the fifth antituberculous

drug, thiacetazone, much less is known, at any rate in English-speaking countries.

In 1946 Domagk and his colleagues[2] in Germany reported that, among a number of thiosemicarbazones, *p*-acetylaminobenzaldehyde thiosemicarbazone was the most active against tubercle bacilli *in vitro* and also in experimental animals.[3] Thiacetazone, as it is now officially called, has in the past suffered from a surfeit of names. In Germany it began as "conteben" or TBI-698: other proprietary names are "berculon A," "seroden," "thioparamizone," "tebasid," and "thiotebesine." The action of thiacetazone on tuberculous infection in mice was confirmed by Levaditi,[4] who found it inferior to streptomycin but comparable in effect to P.A.S. Experiments by Behnisch and his colleagues[5 6] suggest that the sulphur atom is essential for antituberculous activity, that compounds derived from aldehydes are more effective than those obtained from ketones, and that the aromatic aldehydes yield more potent compounds than the aliphatic aldehydes. The introduction of substituents into the aromatic ring is also said to increase activity. Hoggarth and his colleagues[7] examined a number of thiosemicarbazones and found that, though thiacetazone was effective in mouse infections, yet *p*-ethylsulphonylbenzaldehyde thiosemicarbazone (termed by the Germans Tb III. Be 1374 and in this country "berculon B") was even more effective and certainly surpassed P.A.S. though not streptomycin. The relationship between the two substances can be seen from the structural formulae.



Thiacetazone.



p-Ethylsulphonylbenzaldehyde thiosemicarbazone.

Hamre and his co-workers[8] examined nearly 100 thiosemicarbazones and related compounds and found that only eight were active against tuberculous infections in mice. In order of potency the substituents of 3-thiosemicarbazone are: ethylsulphonyl, *iso*-propylamino, acetamido, dimethylamino, nitro, sulphamyl, methoxybenzaldehyde. Although only compounds active *in vitro* have an effect in the mouse, there is no correlation between the inhibitory activities *in vivo* and *in vitro*.[9]

Thiacetazone can be given either by mouth or parenterally. It is not very soluble in water, but solutions can be made up in propylene glycol and some acid amides. A method of estimating the amount of thiosemicarbazone in body fluids has been worked out by Spinks.[10 11] The agreement between the amount in the blood and the therapeutic effect suggests that the thiosemicarbazones act directly rather than after conversion in the body. This is borne out by the fact that thiacetazone, in addition to inhibiting the growth of tubercle bacilli *in vitro*, causes morphological changes such as abnormal size, granular disintegration, and the appearance of delicate threads. Bacilli first of all lose their capacity to take the Ziehl–Neelsen stain and finally the Gram stain. It seems probable that thiacetazone combines with one of the blood proteins. One way in which it is superior to P.A.S. is that it is not inactivated by *p*-aminobenzoic acid.

From 1947 onwards a very large number of cases of all forms of tuberculosis have been treated in Germany.[12 13] Many of the treated cases, however, provide little or no real evidence of cure, since there were no controls and the period of observation was short. In Germany the assessment of the value of a new drug has been specially difficult because of widespread malnutrition and a shortage of *x*-ray films. Hinshaw and McDermott[14] reported their observations after visiting 10 of the larger German centres where the drug has now been in use for four years. The best results have been seen in "fresh-exudate" types of pulmonary infection and in laryngeal and intestinal tuberculosis. In some cases of tuberculous eye infection cures have been claimed.[15] In miliary infections and in tuberculous meningitis results are far inferior to those obtained with streptomycin. The dosage used has been low—25–50 mg. daily for the first week or two, with a gradual increase to 200–300 mg. daily if the patient can tolerate it. Some workers prefer a maximum of 150 mg. daily. Treatment must be continued for 6 to 12 months.

While the therapeutic activity of thiacetazone still awaits critical appraisal, there is evidence to show that it is by no means non-toxic. Anorexia, constipation, malaise, dyspepsia, palpitation, dizziness, pain in the eyes, photophobia, blurred vision, and headache often occur, but vomiting is less common. The more severe reactions, occurring it is said in about 0.4% of cases, consist of toxic erythemata, conjunctivitis, cerebral oedema, anaemia, and granulocytopenia. Fatal jaundice of hepatotoxic origin has been reported. Oedema of the brain with severe fatty degeneration of the liver parenchyma was seen by

[1] Medical Research Council investigation reported in the *British Medical Journal*, 1950, **2**, 1073.
[2] *Naturwissenschaften*, 1946, **33**, 315.
[3] Domagk, G., *Nord. Med.*, 1948, **39**, 1322.
[4] *Pr. méd.*, 1949, **57**, 519.
[5] *Angew. Chem.*, 1948, **5**, 113.
[6] *Amer. Rev. Tuberc.*, 1950, **61**, 1.
[7] *Brit. J. Pharmacol.*, 1949, **4**, 248.
[8] *J. Bact.*, 1950, **59**, 675.
[9] Donovick, R., Pansy, F., Stryker, G., and Bernstein, J., ibid., 1950, **59**, 667.
[10] *Brit J. Pharmacol.*, 1949, **4**, 256.
[11] Moss, D. G., *Lancet*, 1950, **2**, 570.
[12] Domagk, G., *Amer. Rev. Tuberc.*, 1950, **61**, 8.
[13] Mertens, A., and Bunge, R., ibid., 1950, **61**, 20.
[14] Ibid., 1950, **61**, 20.
[15] Chylimoniuk, M., *Przegl. Lek.*, 1950, **6**, 95.
[16] *Mschr. Kinderheilk.*, 1949, **97**, 349.
[17] *Klin. Wschr.*, 1950, **28**, 373.
[18] *Arch. Otol., N.Y.*, 1949, **53**, 289.
[19] *Proc. Mayo Clin.*, 1950, **25**, 160.
[20] *Schweiz. med. Wschr.*, 1950, **80**, 373.
[21] *Lancet*, 1950, **2**, 286.

Heepe[16] in three children who died after treatment with thiacetazone. A tendency to haemorrhage or purpura is an early danger signal. Other warning signs are a fall in the number of erythrocytes or white cells, a fall in blood sugar level, and a rise in icterus index. During treatment the urine should be examined at frequent intervals for cells, casts, albumin, urobilinogen, and sugar. As the drug is a liver poison the diet should be rich in protective foods. Intercurrent infections likely to throw an extra strain on the liver parenchyma would be a contraindication to treatment. The possibility of bacilli developing resistance against thiacetazone has not yet been fully examined, but Auersbach and Schütz[17] believe that thiacetazone-resistant strains can occur. These are then also resistant to other thiosemicarbazones. In order to diminish the toxicity of thiacetazone attempts have been made to combine it with other drugs. The combination of sulphathiazole and thiacetazone was highly toxic and has been abandoned. Lepri and Capalbi[18] showed that in experimental ocular tuberculosis P.A.S. and thiacetazone given together acted synergistically. More recently Karlson and his colleagues[19] have suggested that streptomycin combined with thiacetazone is more active than either drug alone, but Moeschlin and Demiral[20] deny this and find the combination of streptomycin and P.A.S. much more effective.

It is obvious that, although streptomycin is far more active than thiacetazone, nevertheless the thiosemicarbazones are a group of compounds with undoubted tuberculostatic properties. Their true role in human tuberculosis can be indicated only by carefully controlled investigations in which they are compared with streptomycin and with P.A.S. The possibility of synergistic activity between these compounds and thiacetazone also requires much fuller study. In the meantime it may be noted that Ryrie[21] has obtained encouraging results in 10 cases of leprosy after treatment for four months. With doses of from 50 to 150 mg. of thiacetazone daily there was no tendency to lepra fever, which is a danger with sulphones. In addition, the mental depression and slowing of cerebration so characteristic as effects of sulphone therapy were absent.

CONGENITAL MALFORMATIONS

Pliny said that "Nature creates monsters for the purpose of astonishing us and amusing herself." Up to quite recent times it was widely believed that congenital abnormalities were the result of impressions received by the mother during pregnancy. Empedocles, Plato, and Hippocrates all held that a severe fright during pregnancy might leave its imprint on the unborn foetus.[1] In 1726 George I sent his chief surgeon to investigate the story of Sarah Toft, of Godalming, who was said to have been delivered of 17 rabbits: when five weeks pregnant she was alarmed by a rabbit which suddenly sprang up in front of her as she walked in a field.

In recent years a great deal has been learned about the aetiology of congenital anomalies. Warkany,[2] Murphy,[3] and Kiskadden and his colleagues[4] have all reviewed the subject in detail. Warkany described the experimental production of congenital deformities—such as cleft palate, horseshoe kidney, eye defects, syndactyly, and other deformities of the skeleton—by exposing the pregnant animal to gross vitamin A, riboflavin, copper, or iodine deficiency, or to the noxious action of various poisons, such as selenium, lithium, and *x* rays. In a more recent paper Warkany and Wilson[5] reported that gross vitamin-A deficiency can cause cardiovascular anomalies, such as septal defect, and anomalies of the aortic arch and pulmonary artery. Hypervitaminosis A also causes abnormalities in developing bone, as Mellanby[6] has shown in a report which recently appeared in this *Journal*. In addition, there is evidence that skeletal abnormalities can be induced in developing chickens by the injection of insulin into the yolk of the eggs.[7] Murphy[3] discussed the genetic and statistical aspects of congenital deformities. He states that the chance that any couple will have defective offspring is 1 in 200. The likelihood that a second malformed child will be born to parents that have had one is increased 20–25-fold. The hazard of malformation increases with the age of the mother, rising progressively year by year after the mother has passed 30. The risk of congenital deformities of the foetus being caused by virus infections during pregnancy, particularly rubella, is now well known. Anomalies of placentation, such as ectopic pregnancy and placenta praevia, as a cause of deformities is also recognized.

Recently Record and McKeown[8-10] have brought new facts to light during a large-scale field study in Birmingham. They chose congenital deformities of the central nervous system for study, partly because this group would be expected to provide adequate numbers for investigation, and partly because errors of diagnosis were unlikely. They recorded observations on the aetiology of 930 consecutive malformations of the nervous system which were the cause of stillbirth or first-year death between 1940 and 1947. These constituted 0.59% of the total births in the city in that period. The types of malformation were hydrocephalus (150), spina bifida (389), anencephaly (366), and other defects (25). In 8.3% of the infants defects of other organs were also present. The homes of the mothers of these children, and of those in a control group obtained by selecting every 200th name in the registers of live and still-births for the same period, were visited by a team of investigators. It was found that the risk of a congenital

1 Gordon, B. L., *Romance of Medicine*, 1945, Philadelphia.
2 *Advances in Pediatrics*, 1947. London, vol. 2, p. 1.
3 *Congenital Malformations*, 1947, Philadelphia.
4 *Int. Abstr. Surg.*, 1949. **88**, 1.
5 *Pediatrics*. 1950, **5**, 708.
6 *British Medical Journal*, 1950, **2**, 535.
7 Duraiswami, P. K., ibid., 1950, **2**, 384.
8 *Brit. J. soc. Med.*, 1949, **3**, 183.
9 Ibid., 1950, **4**, 26.
10 Ibid., 1950, **4**, in the press.