It is necessary to recognize that histamine is a degradation product (by decarboxylation) of the amino-acid histidine, and acts after the manner of a powerful drug. Its presence in a peptone is a drawback, as it not only may entail a limitation of the dosage, but is itself quite useless in the immunizing process, if not actually harmful. It was found by Hanke and Koessler that peptone which was perfectly histamine-free produced the typical peptone shock. Histamine shock has indeed the more obvious features of peptone shock, but is shorn of certain essential attributes of the latter—namely, extensive katabolism of body tissues and incoagulability of the blood (supposed due to antithrombin formation from the interaction of peptone and hepatic cells).³ Ringer and Underhill⁴ were unable to produce any increase in tissue katabolism by shock doses of histamine enormously greater than those contained in a toxic dose of Witte's peptone. Further, histamine is unable to produce swelling of the liver in dogs, or to produce pyrexia, or to desensitize. Histamine has been occasionally detected in the intestines, but whether it escapes the action of the liver and produces the symptoms of disease is an open question. It certainly can be swallowed in considerable amount, comparatively speaking, without the production of any symptoms. But in the katabolism of tissue associated with anaphylactic or anaphylactoid shock it is quite possible that histamine may be produced where cell-oxidation ceases, just as it is supposed to be formed in the tissue destruction leading to wound shock.

The dermal (scratch) test may give evidence as to the presence of histamine in a peptone (conc. solution), as all individuals give a marked though varied response to extremely dilute solutions of histamine. For testing purposes one of Burroughs, Wellcome and Co.'s ergamine tabloids may be dissolved in water or saline in various dilutions and used as a control. A peptone giving a wheal of 0.4 cm. and upwards in diameter in a series of cases may be suspected, the size of the wheal depending on the sensitiveness of the patient to histamine, though it must be remembered that sensitiveness to the peptone itself may also be present. Of the peptones I have tested in this way, the largest wheal (up to 1 cm.) has been constantly given by Parke, Davis's peptone (which contains no primary proteose). Confirmatory evidence is afforded in the immediate histamine effect produced by the intravenous injection of very small doses of this preparation.

A patient may be hypersensitive to both peptone and histamine, but the same patient may react differently to histamine on separate occasions, owing to unknown causes; also, the dermal and constitutional reactions do not always correspond. Sometimes intradermal tests are made, but they are usually unnecessary and may be dangerous, unless a very dilute (2 per cent.) solution of the peptone or suspected peptone be used, and then only 0.1 c.cm. should be injected. The injection of a strong solution may cause histamine shock. Also, if after a negative intradermal injection the ordinary intravenous injection be soon made, the two may summate and cause shock. According to Dr. Chandler Walker,⁴ intradermal injections are very erratic, far too sensitive, and practically non-specific.

Ordinarily, therefore, and especially for those requiring a higher dose of proteose—sufficient, that is, to produce a slight constitutional reaction—the Armour No. 2 peptone† should be employed, which, in my experience, never gives the histamine effect. It will be found that the maximum dosage will approximate 2 to 2.5 c.cm. of the 5 per cent. solution. Witte's peptone is of particular value in certain cases owing to the nature of its proteoses, but it is best given diluted with a weaker peptone, as recommended in my last paper.⁵ But the Armour peptone (intramuscular or intravenous) gives the best results in the majority of cases, and may be safely administered to the youngest child. Should toxic symptoms unexpectedly supervene, suspect contamination of the solution—a not infrequent occurrence. It may be added that a satisfactory immunizing process is characterized by a slight leucocytosis, particularly as regards the large mononuclears, and by increase in the haemoglobin and red cells.

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* Evidence of a new kind, contrary to this view, has lately been advanced (*Proc. Roy. Soc.*, Series B, vol. 93, p. 367).

† The Armour Company have given an assurance that this peptone will be maintained of a uniform composition.

A CASE OF NON-RHEUMATIC AORTIC STENOSIS
IN A YOUNG SUBJECT.*

BY

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DR. L. GALLIVARDIN has recently described in an interesting paper a group of cases of aortic stenosis in young persons which he believes to be non-rheumatic in origin.¹ The case I bring before you seems to belong to this group.

The special features of the group are:

1. Aortic stenosis with loud murmur and marked thrill in young persons.
2. The stenosis generally "pure"—that is, unaccompanied by regurgitation, or, if aortic regurgitation coexists, its murmur much less marked than the murmur of the stenosis.
3. A long period without symptoms.

The causation Dr. Gallivardin considered doubtful: some cases he thought might be of congenital origin; most, he suggested, might be due to a post-natal valvulitis of unknown nature. Eight male cases were described in his paper, aged respectively 21, 25, 19, 20, 17, 19, 21, and 25. Of these the first only had been also observed at an earlier age—namely, at 7 or 8.

H. C. P., aged 17½, a bricklayer's apprentice, a florid, well-nourished, healthy-looking, intelligent lad, was sent to me by Dr. Waite of Heavitree, complaining of shortness of breath on exertion. This had been noticeable for six months, but only troublesome for three months, during which he had been put on a man's job, carrying hods and working eight hours a day. He had had no pain, faintness, giddiness, cough, or blueness on exertion. At 11 years old a school doctor had forbidden him to play football on account of "incurable" heart trouble, but he had continued to play because he felt no ill effects from doing so. The boy has never had rheumatism, chorea, or scarlet fever. No doctor attended his birth. At nearly a year old he was in this hospital for large glands in his neck which subsided without operation; no mention is made in the surgical notes of any tonsillitis, nor, unfortunately, of the state of the heart. As a child he had whooping-cough and chicken-pox. On leaving school he worked first as a compositor, then as an Army Pay Corps messenger, then for sixteen months as a tailor's porter, with much bicycling and some lifting of heavy weights, finally at his present job, which has proved too much for him. He has never had any serious accident or sudden overstrain; influenza in 1918 was the only illness since childhood in which he needed a doctor.

There is no family history of acute rheumatism or chorea. His father is a strong-looking man of 55 who has had some "rheumatic gout" for ten years, never syphilis. His mother died of phthisis at 46; she was subject to "fainting attacks," but was not said to have heart disease; she had no miscarriages. A brother of the patient in the army died of phthisis at 26. Two sisters and another brother are alive and well; the surviving brother has had his tonsils removed, but is stated never to have had acute tonsillitis.

The circulatory condition is as follows: Pulse regular (84), not "water-hammer," giving the anacrotic, flat-topped tracing of

aortic stenosis. After brisk exercise the rate rises to 108, but drops back to 84 in two and a half minutes. There is visible pulsation above the manubrium and clavicles, but little further up the neck. In the erect position the heart's apex beat is in the fifth space, half an inch inside the left mammary line, and the dullness reaches transversely from that point to three-quarters of

FIG. 1.—a, a, Limit of thrill in upright position. b, b, Ditto in recumbent position. c, c, Limit of systolic murmur, upright position. x, Maximum point of murmur and thrill.

an inch to the right of the mid-sternal line—practically a normal width. Over the upper part of the chest there is a marked systolic thrill and a loud, rasping systolic murmur; both have their maximum close to the right sterno-clavicular joint and just over the manubrium in the neck; the murmur is heard in the carotids up to the ear, and almost all over the chest. Fig. 1 shows the area

* Read at a meeting of the Exeter Division of the British Medical Association, February 17th, 1922.

of the thrill and the lower limits of the murmur. There is also a much softer, fainter diastolic murmur, whose area is shown in Fig. 2. When I first saw the patient this diastolic murmur was heard with difficulty with the double stethoscope, a little better with the straight stethoscope, and surprisingly easily by the ear laid directly on the chest. It is interesting to note that Dr. Gallivardin made the same observation on one of his cases. When a deep breath was taken and held the diastolic murmur disappeared, which I think indicates a very slight degree of regurgitation. The femoral pulses are normal and Duroziez's sign is absent. A skiagram shows a fairly normal-sized heart, but with a rather dilated aorta, and with the screen this aorta is seen to pulsate actively—a condition which, Vaquez and Bordet consider, suggests congenital aortic stenosis.² The second sound is audible over the right clavicle.

Fig. 2.—Area of diastolic murmur. *d, d*, in upright position; *e, e*, in recumbent position.

There is no clubbing of fingers or toes. The right tonsil is chronically enlarged, a fact of which the patient was unaware. The other organs, including the ocular fundi, are normal.

The diagnosis of an aortic stenosis with regurgitation is here so plain that no discussion is needed. The actual degree of stenosis cannot be great, judging by the pulse, the size of the heart, and the symptoms, although the murmur is what might be suitably called "extravagant." The regurgitation must be very slight, judging by the pulse, the presence of the aortic second sound in the neck over the right clavicle, the size of the heart, the characters of the murmur, and the symptoms. No other cardiac lesion has been detected.

I do not think we can reasonably consider that the valve defect is in this case post-rheumatic. It clearly is not traumatic or syphilitic. So the question to decide becomes, Is the condition of congenital origin, or has it arisen between birth and 11 years of age from some unknown form of valvulitis? I would venture to suggest that it is of congenital origin, and that the whole group, to which it seems to belong, has a similar etiology.

First, clinically when one finds what I have called an "extravagant" murmur with little cardiac enlargement or disturbance, one thinks of congenital heart disease. And this is reasonable, for in such cases an undamaged muscle is driving the blood through sharply defined orifices or against clean-cut obstacles. The stenotic murmur in this group is, in Dr. Gallivardin's words, "intense, rude, râpeux," even "énorme," and is much louder and more widely audible in this boy than in the cases of acquired aortic stenosis of later life to which one is accustomed. The only comparable aortic stenotic murmur I have met with was in another young male of 19 who had recently been passed as a first-class life on account of his healthy appearance and freedom from symptoms.

Secondly, there seems to be a series of similar cases reported in children, and these have been generally diagnosed as congenital. My patient's lesion was detected at 11. One of Dr. Gallivardin's cases was declared to have heart trouble at 7 or 8. MM. Queyrat and Mouquin describe an apparently identical condition in a boy 5 years and 8 months old which they call congenital, and in the discussion upon it M. Barié recalled a case observed in a child by himself, and quoted another which had been reported on at 4 years of age.³

Thirdly, lesions capable of causing such signs, though rare, are known to morbid anatomists. Apart from coarctation of the aorta and aortic hyperplasia, which do not concern us here, there are three forms of congenital aortic narrowing—namely, (1) subvalvular aortic stenosis, a few millimetres below the valves, which, unless endocarditis supervenes, allows of survival to adult life with few or no symptoms, but with the physical signs of aortic stenosis; (2) stenosis due to prenatal valvulitis, seldom surviving birth, although, as Hirschfelder suggests, "probably many of the milder cases escape detection";⁴ and (3) stenosis due to valvular malformation, which, if valvulitis does not follow, is compatible with many years of life. Peacock says: "I have seen only two valves at the aortic orifice occasionally in persons who have died in advanced life, and frequently in middle age, without the segments having presented any appearances of more recent disease; and similar facts have been noted by others."⁵ Such a condition (two valves only) would seem capable of accounting for a loud systolic murmur, a retained second sound, and a much slighter diastolic murmur, as in the case before us. It is less easy to imagine the same picture being presented by the result of post-natal valvulitis.

Lastly, although in my case I cannot prove that the lesion is congenital, I can find no history of any condition known to produce valvulitis. The enlarged tonsil might be held to indicate some chronic infection, but we have no evidence that it antedated the murmur. The glands in the neck were probably tuberculous, seeing that his mother and brother died of phthisis. In Dr. Gallivardin's cases I can find no proof that the murmurs described had not dated from birth, and it seems safer to assign a known origin than to invoke an unknown one.

The question is by no means merely academic. If chronic valvulitis is responsible for the condition we must fear its continuance. If a malformation is the cause, provided valvulitis does not supervene, we may hope for many years of life. Although at the moment we cannot come to any final conclusion, it seems worth while raising the point, in order that our congenital aortic stenoses may perhaps be more persistently followed, and that, in the rare opportunities of autopsy, attention may be more closely directed to the possibility of congenital defect.

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OBSERVATIONS ON TWO AND A HALF YEARS' ANTENATAL WORK.

BY

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My object in recording these observations is to show the great value of the antenatal clinic as an educational factor and its possibilities from the point of view of preventive medicine. My remarks are directed to such cases of pregnancy as are commonly classed as normal, for the value of the antenatal clinic in the early diagnosis of gross abnormality has already been sufficiently emphasized in current medical literature. It has been estimated that 40 per cent. of women out-patients suffer from some form of ill health directly or indirectly due to child-bearing. My experience has convinced me that a large part of this ill health is due to neglect of the so-called minor maladies of pregnancy, and that its prevention is largely a matter of patient individual teaching such as can be carried out at antenatal clinics. Of 138 cases 42.8 per cent. suffered from constipation, 36.5 per cent. from flatulence and heartburn, 31.7 per cent. from varicose veins (severe), and 52.38 per cent. from vomiting. The milder degrees of vomiting were not always entered. Out of 300 mothers whom I personally interrogated, 67, or 22.3 per cent., had never once vomited during pregnancy.

All these women received detailed teaching on hygiene—principally on clothing, diet, and exercise; no medicines were advised except such as can fairly be called "domestic remedies," in order that the antenatal clinic might retain its character as a teaching centre and not encroach in the slightest degree on the province of the general practitioner. Had any case not responded to these simple measures she would have been referred to her own doctor; but out of over 200 cases seen during two and a half years this necessity did not arise, though in some the vomiting was severe enough to interfere with sleep and materially to affect nutrition. In marked numerical contrast to the above figures are the more serious disorders which were treated apart from the clinic and exclusive of venereal disease—namely, there were four cases of contracted pelvis and one of albuminuria.

But apart from improving the health of individual mothers and babies, we are all keenly aware of the need for research in antenatal physiology and pathology. We need statistics on conceptional rate, on intrauterine death rate (both foetal and full-term), and on still-birth rate, as well as what has been called intranatal and neonatal death rates. We need, too, both analytical and experimental statistics on the effect of different toxins, x rays, etc., on the germ cell or on the foetus at all stages of its development. Clinics efficiently equipped