PREVENTION and TREATMENT

of

ASTHMA

by PHYSIOLOGICAL METHODS.

by HENRY STEWART RUSSELL B.Sc., M.B., Ch.B.

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PREVENTION AND CURE OF ASTHMA.

Introduction:

Asthma may be defined as difficulty in breathing due to obstruction in or about the bronchi and bronchioles. Various forms are described by some writers, but the common feature in all consists of an acute dyspnoea, commonly occurring in the early morning, which passes off more or less suddenly, leaving the organs apparently healthy.in some cases. This type may be called the pure spasmodic. Other cases havea certain amount of "bronchitis" between attacks. Cases in which the attack is commonly precipitated by exposure to a known foreign protein or chemical substance are described as allergic or sensitive, in contradistinction to the remaining cases which are described as nonsensitive.

Asthma in adults is afebrile but in children pyrexia frequently occurs. The recurrent bronchitis of children is undoubtedly asthmatic in nature. Associated conditions in children are laryngismus stridulus and eczema (Besnier's prurigo).

The characteristic features of the attack are the extreme difficulty of breathing, the distended resonant chest with many rhonchi and the resolution of the attack in most cases by the coughing up of a greater or less amount of sputum which contains eosinophil leucocytes, and in some cases Curschmann's spirals and Charcot - Leyden crystals.

Of the cause of asthma many opinions have been held. Prior to 1903 spastic contraction of the inspiratory muscles was thought by some to be the explanation of the attack. Brodie and Dixon's work concentrated attention on the bronchospasm, and a neurotic origin was commonly accepted. Other explanations have been "toxaemia", calcium deficiency, alkalosis, acidosis, nasal origin and heredity. More recently laboratory anaphylaxis has directed attention to protein sensitisation and allergy has been put forward as the main cause. The reason for the allergy has not been explained.

The Chicago group hold that asthma is due to three factors, basic toxicosis, irritable nervous system and ethmoid irritation. The nature of the toxicosis is obscure. Cameron in this country holds similar views. Adam considers

that asthma is primarily a toxaemia, due partly to intestinal putréfaction, but mainly to an error in nitrogenous metabolism associated with excess of carbohydrate in the diet. He suggests that abnormal products of protein metabolism cause the attack. Excellent results are claimed for methods of treatment based on these lines. It does not of course follow that the theoretical basis is sound.

It is evident that the allergic theory does not give a full explanation. Even in laboratory animals sensitisation is not an invariable result of the injection of a foreign protein. Some species of animals are remarkably resistant to the process, and the resistance of an animal can be influenced by alterations in diet.[1] To say that asthma is due to allergy does not take us very far. It may enable us to desensitise a patient to one protein or to remove him from that protein, but does not guarantee that he will not become sensitive to another. Multiple sensitisation is the rule rather than the exception.

The discussion as to the causation of asthma seems to require the application of William of Occum's razor. "Entia non sunt multiplicanda praeter necessitatem".

I have attempted to arrive at a theory which would account for the known facts without conflicting with any of them. My view is that asthma and the allergic state are due to subnormal action of the sympathetic nervous system, caused by inhibition of the suprarenals, and that this condition is frequently due to absence of the normal physiological stimulant of these glands - cold. Other factors such as the influence of acute infections are important in some cases, but suprarenal inhibition is commonly due to absence of metabolic stress. A thyroid gland defect is frequently associated with the suprarenal deficiency.

Roussel[2] (1929) put forward the conception of thyroadrenal dysfunction to account for urticaria, and described three cases cured by administration of thyreoid extract in 1902.

1. See page 4

2. "Southern m.g." 1929 22, 668 quoted by Bray p.105

Adam describes several cases showing changes post-mortem in the suprarenal glands. One case, a woman who had been receiving large doses of adrenalin had suprarenals from which the medulla had almost disappeared.

THE ALLERGIC FACTOR.

By allergy or anaphylaxis we mean the sensitisation of an animal to a foreign protein by previous exposure of the animal to the influence of the protein. The importance of allergy in the pathology of asthma may have been over-stressed. Coke shows 52% of his asthma cases as sensitive, using skin tests as the criterion. Percentages up to 75% allergic have been claimed by other workers.
The reliability of skin tests is open to doubt.[5] It is commonly found that an asthmatic attack cannot be produced at will by feeding a patient with the substance which produces a positive skin reaction (Vining). However, allergy is responsible for some asthma, no doubt, and it gives us some clues to the cause of the condition.

The phenomena of hypersensitiveness were noticed by Magéndie as early as 1839, but were first fully described by Richet and Portier in 1902. The protein used was "congestin", the toxin of Actineae. Arthus in 1903 described local reactions in rabbits to repeated injections of protein. Rosenau and Anderson claimed to sensitise gainea-pigs to horse serum by feeding with horseflesh, though Besredka was unable to confirm this in the case of milk. Milk, however, is not so "species specific" in its effect as some proteins. The specificity of protein is a remarkable feature of anaphylaxis.[3]

Raw and heated egg albumen behave as different proteins, i.e. one does not sensitise to the other.

Anaphylaxis produces different symptoms in different animals, but the shock is the same whatever proteins are used. In guinea-pigs bronchospasm is the main feature. In other animals vomiting, diarrhoea, oedema of muzzle, micturition, etc. occur. Fall of bloodpressure is constant, and the coagulation time of the blood is increased.

Adam. bibliography 2.
Vining C.W. Personal communication.
Besredka "Anaphylaxis" ch.
cf. case 1 p. 28
5 See Appendix (b)

As Schultz remarked, "All smooth muscle is sensitised", and the shock produces a parasympathetic effect. Gaskell considers that the vagus controls anabolic processes, and that vagus stimulation hastens tissue repair. This has not been demonstrated in the case of other parasympathetic nerves, but the fact may have some bearing on the problem.
Dale has shown that sensitivity can be demonstrated in the excised and washed uterus of the guinea-pig.
Besredka found that atropine would not prevent appearance of shock so that the effect must take place beyond the nerve ending. It may occur in the myoneural junction or in the muscle fibre itself.

The most interesting point about anaphylaxis for our present purpose is the fact that it cannot be produced in every species of animal. It is difficult to sensitize monkeys and very difficult to sensitize rats on normal meat diet. Rats on a bread and milk diet are easily sensitised, which also occurs after adrenalectomy.

Similarly in man, a few are sensitised to strawberries or lobster by an occasional surfeit, but the great majority are not.

Besredka found that anaphylaxis could not be produced under anaesthesia, during intoxication with alcohol or for twenty-four hours afterwards, during starvation or during pregnancy.

Otto in 1906 found that the addition of diphtheria toxin to the sensitising dose of horse serum made a guinea-pig much more liable to anaphylactic shock on the reinjection of horse serum alone. This important observation appears to have been generally overlooked. Diphtheria is known to have an adrenalotoxic action. These results can be tabulated, (see next page).

Hajos[1] (1926) found that thyreoid extract and insulin increased and adrenalin and post-pituitary diminished liability to anaphylaxis. This finding in the case of thyreoid extract is paradoxical and requires confirmation as it conflicts with clinical experience.

1 Immunology 1926 10. 560 quoted by Bray p. 105.
2 Dale "Allergy" p. 49

AGENT	EFFECT	THYROID	ADRENALS.
Milk & bread	increases Anaphyl.	depresses	?
Diphtheria toxin	" "		depresses
Meat	prevents Anaphyl.	stimulates	
Ether	" "		stimulates
Alcohol	" "		"
Pregnancy	" "		cortical lipoid increased
Starvation	" "		" "
Fever [1]	" "	stimulates	" "
Adrenalectomy	increases Anaphyl.		

We find that agents which stimulate the sympathetic system prevent allergy, which produces a parasympathetic action, while agents which depress the sympathetic favour allergy.

In dogs anaphylaxis is said not to occur when the liver is clamped out of the circulation, and to come on when the clamps are withdrawn. The exclusion of the liver will lead to hypoglycaemia which stimulates adrenalin formation. The reestablishment of circulation causes hyperglycaemia and adrenal inhibition.

Oriel describes an increase in urinary acidity and creatinin excretion before an attack, with retention of water and chlorides during the attack, (thyroid action?) and diuresis with excess of chlorides and bases after the attack.[2]

In allergic eczema there is increased sugar tolerance and pigmentation of skin suggesting suprarenal defect.[3]

Enough has been said to indicate that the liability to allergy as well as to asthma may depend on thyroid adrenal insufficiency.

1. Cramer p. 132. N.B. in this case fever is the result of the thyro-adrenal stimulation.
2. Oriel, " Allergy p. 14
3. " " p. 39

THE AUTONOMIC NERVOUS SYSTEM.

As Gaskell first pointed out, when sympathetic and parasympathetic fibres are distributed to the same structure their effects are antagonistic. Speaking generally, sympathetic activity prepares the body for a struggle and increases its powers of defense, while the parasympathetic system aids recovery and causes the performance of acts leading immediately to greater comfort.[1] The sympathetic system is katabolic and the parasympathetic system is anabolic.

Eppinger and Hess,[2] largely from the study of pharmacological effects, put forward the interesting theory that in certain persons the balance between these systems may be disturbed producing on the one hand a vagotonia and on the other a sympathicotonia. This conception has been challenged on various grounds, the most damaging criticism being based on the behaviour of the sweat glands. As these structures are of clinical importance it may be well to consider the matter more fully.

As Langley[3] has shown the nerve supply of the sweat glands arises entirely in the sympathetic chain. Leaving the cord by the white rami communicantes from the second dorsal to the third and fourth lumbar segments these fibres pass into the sympathetic chain. From the ganglion cells grey rami pass into the various spinal nerves to be distributed to the skin surface. Now the curious feature is that although these fibres are undoubtedly sympathetic from the anatomical viewpoint the glands are caused to secrete by pilocarpine, which is a parasympathetic stimulant.

Eppinger and Hess therefore suggested that sweating was a vagotonic symptom. The effect of pilocarpine is inhibited by atropine but not by nerve section, i.e. it is a peripheral effect. Sweating in response to thermal stimulation is however mainly central in origin.

Langdon Brown holds that it is unjustifiable to prefer pharmacological evidence to anatomical and dismisses the suggestion as special pleading.

1 Cannon. "Bodily Changes in Pain, Hunger, Fear and Rage". London 1916. Quoted by Langdon Brown.
2 Eppinger and Hess. "Journal of Mental and Nervous Diseases" vol. xli 1914 vol xlii 1915. quoted by Langdon Brown.
3 Quoted by Starling.

However, there are good physiological grounds for considering the possibility. Adrenalin, although a sympathetic stimulant, does not produce sweating, which is a delayed response to effort, and does not occur until the body temperature is appreciably raised. On the other hand, thyreoid extract does produce sweating.

There is strong evidence that sympathetic action is concerned with heat production while parasympathetic action favours heat loss. It is also apparent that two types of sweating have to be considered, "hot sweats" and "cold sweats", the latter are produced in states of shock and by psychic stimuli. The former is a cooling mechanism and probably a parasympathetic effect functionally. The cold sweat is not primarily a cooling effect, but by reducing the blood volume and increasing haemoglobin percentage temporarily it may be a preparation for effort. Consideration of the fevers shows that sweating generally occurs after the phase of excessive heat production has ceased.

The case of Graves' Disease at first sight suggests a sympathetic origin for the sweating, but it is probable that this is a secondary effect due to rise of body temperature. Similarly the dry skin of myxoedema would be regarded as secondary to the subnormal body temperature and as a measure of heat conservation. I have found that sweating does not occur when thyreoid administration is accompanied by ephedrine, which is a sympathetic stimulant and might be expected on current theory to increase sweat secretion.

An explanation of these various phenomena is suggested by the local action of adrenalin on injection.[1] If a current of hot air is directed on the portion of skin surrounding the injection it is found that the area containing adrenalin commences to sweat more readily than the surrounding skin, although no sweating occurs while the skin is cold. Therefore, one may deduce that sweating requires vasodilatation to be present before sympathetic stimulation can become effective. In other words, sweating is not a purely sympathetic effect but requires an associated parasympathetic effect for its production.[2]

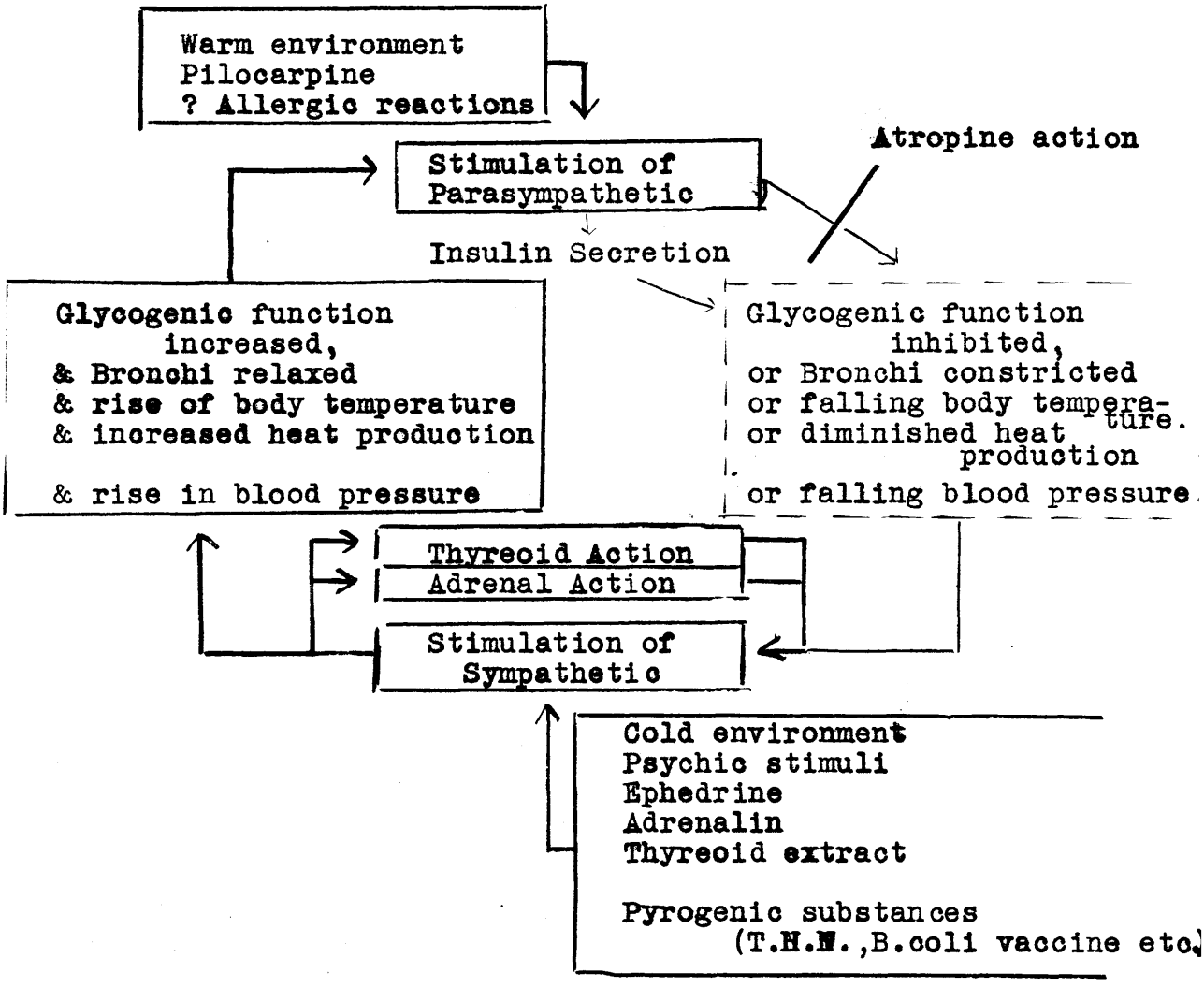
The balance between sympathetic and parasympathetic

1. Frenz. Wiener klin. Woch. 1920 32. 1009. Lehrbuch of Pharmac, p. 61.

ERRATUM. For "injection" read "application by kataphoresis".

2. cf. Sweating in the hot room after Turkish bath is greatly increased by drinking cold water, i.e. Sympathetic stimulation is required in addition to external heating. (Cold drinks Stimulate sympathetic — See Goodman Lewis

activity can be represented by a diagram of this type.



SCHEME OF AUTONOMIC BALANCE.

It will be noticed that whereas parasympathetic stimulation controls various phases of metabolism to different degrees in different circumstances, sympathetic action tends to produce a syndrome of fairly constant type as might be

expected from its character as an emergency mechanism. It will also be noticed that the scheme postulates a parasympathetic reaction to sympathetic stimulation and vice versa. This is justified by the observation that the effects of the one mechanism are the stimuli for the other. This interaction is no doubt the explanation of the remarkable constancy of biochemical findings in healthy people.

EOSINOPHILIA.

Neusser claimed that pilocarpine caused eosinophilia while atropine lead to its disappearance. Adam found that a cold bath lead to diminution of eosinophilia. These observations suggest that eosinophilia is a stigma of vagotonia. In other conditions in which eosinophilia is found adrenal changes are known to occur. For instance, Addison's Disease and intestinal worm infections are both associated with eosinophilia, and in the latter condition Bedson[1] found reduction of cortical lipoid. Convalescence from acute febrile disease is occasionally characterised by eosinophilia. Bezanson and Bernard[2] regard the eosinophil as more closely related to the connective tissues than to the blood cells, and note its association with processes of repair.

MECHANISM OF BREATHING.

In order to understand the nature of the "bronchospasm" in asthma we must try to appreciate what happens in normal breathing. The essential anatomical facts are stated by Starling to be as follows:-

"The trachea, a wide pipe ($\frac{3}{4}$" diameter) about $4\frac{1}{2}$" long, divides below into two main bronchi, and these subdivide again and again becoming gradually smaller. The terminal ramifications or bronchioles open into rather wider parts, the infundibula, the walls of which are beset with a number of minute cavities, the alveoli. The larger tubes are kept patent by rings of cartilage in their walls. The smaller tubes have no cartilage."

1. Cumer h. 121

2. Bray h. 151

With inspiration the capacity of the thorax is increased, and air enters the trachea and bronchi until atmospheric pressure is reestablished in the system, the reverse occurring during expiration.

The musculature of a bronchus is almost entirely composed of circular fibres. ~~surrounding it~~. A few longitudinal fibres are described, but do not appear important. The elastic tissue of the bronchi is longitudinally arranged, without circular fibres. The arterial supply comes from the bronchial arteries, branches from the thoracic aorta, either directly or from the first aortic intercostal artery. These vessels form a plexus in the muscular coat of the bronchus, which communicates by perforating branches with a submucous plexus. Ciliated mucous membrane is continuous through the trachea and bronchi.

It has been shown that the bronchi are constricted by parasympathetic fibres running in the vagus, and that this nerve (in some animals, e.g. cat) also contains dilator fibres which respond to drugs in a similar manner to sympathetic nerves.

The bronchial musculature is well developed, and must have some function other than the production of asthma. Coke suggests that it contracts during normal expiration, in order to increase the distension of the alveoli. Adam states that bronchi dilate during inspiration, when seen through the bronchoscope, and suggests that the bronchioles behave in the same way. Hudson[1] demonstrated that this inspiratory dilatation occurs in the smallest bronchi also.

It appears to have been assumed that this behaviour of the bronchial muscle is due to active alteration in tone, but it would appear more probable that the inspiratory dilatation is purely passive, and is likely to be resisted by vagus action.

What are the factors influencing the size of the bronchi apart from the bronchial muscle?

A. The most important factor is the elastic pull of the lung. Even at the end of expiration the lung is in a stretched condition, and can be shown to produce a "negative pressure" of 6 mm. of mercury in the cadaver. When fully distended the pull may equal 30 mm. of mercury. As there is no circular layer of

1 Bibliography 16.

elastic fibres supporting a bronchus this pull must tend to cause a dilatation. At intermediate positions the elastic pull must be proportionate to the degree of expansion of the thoracic cavity. Hooke's law states that stress is proportionate to strain for elastic substances.

B. Intrabronchial air pressure. While the bronchioles are patent the air pressure within the bronchi must approximate fairly closely to the alveolar pressure. Although the terminal bronchioles are small pipes (·2 mm. in diameter) their cross-sections aggregated together are probably equal to or greater than that of the trachea, so that the obstruction offered to the passage of air will not suffice to maintain any great pressure difference. If the bronchioles are occluded from any cause the bronchial pressure will be nearly atmospheric, and will exceed the thoracic pressure during inspiration, being less than the thoracic pressure during expiration. During forced breathing these pressure differences may be as much as +87 mm. Hg. expiration and -57 mm. Hg. inspiration.

C. The bronchial arteries, being in ring formation round the bronchi, will tend to prevent collapse of the tube. They contain blood at a pressure of 120 mm. Hg. systolic. The variation of blood pressure with respiration is not sufficient to alter this factor to any great degree, but backpressure on the pulmonary veins during forced expiration may have some slight effect in increasing patency. This would be counteracted by engorgement of the submucous plexus causing swelling of the mucous membrane.

D. Swelling of the mucous membrane may occur with an increase in pulmonary venous pressure, and is found in passive congestion of cardiac origin.

To sum up, the most important single factor acting on the bronchi normally is the elasticity of the lung, which puts a strain on the bronchial muscle varying continually eighteen times each minute from six to thirty mm. Hg.

We are entitled to assume that bronchial muscle responds to this mechanical stimulation in a similar manner to other smooth muscle. The function of these circular fibres is the prevention of undue dilatation of the bronchus while the lung is expanded, and information may be obtained as to its action from a study of Sherrington's work on "Stretch reflexes". Working with skeletal muscle he found that a moderate stretching force induced an increase of tension in the muscle which could be maintained without fatigue for as long as half an hour. When the stretching force is removed the muscle relaxes. (This response to stretching depends on the integrity of the nerve supply, but can be obtained in the decerebrate animal).

Something of the same kind would appear to be present in the bladder muscle, though in this case postural activity is adapted to maintain the same tension in the wall irrespective of the volume of the contents. Smooth muscle is said to be capable of some degree of postural activity independently of nervous impulses, though nerve control is of chief importance.

Adapting this knowledge to the bronchial muscle we may deduce that during inspiration, while the bronchi tend to expand under the elastic pull of the lung and to a less extent under the internal pressure of air, vagus impulses are normally acting to increase the tone of the bronchial muscle. The bronchi may dilate slightly or may contract, according to the accuracy with which the pull is balanced.
During expiration the elastic pull is progressively diminished, until it reaches a minimum during the respiratory pause. In this phase then, sympathetic impulses will cause a gradual relaxation of the bronchial muscle.

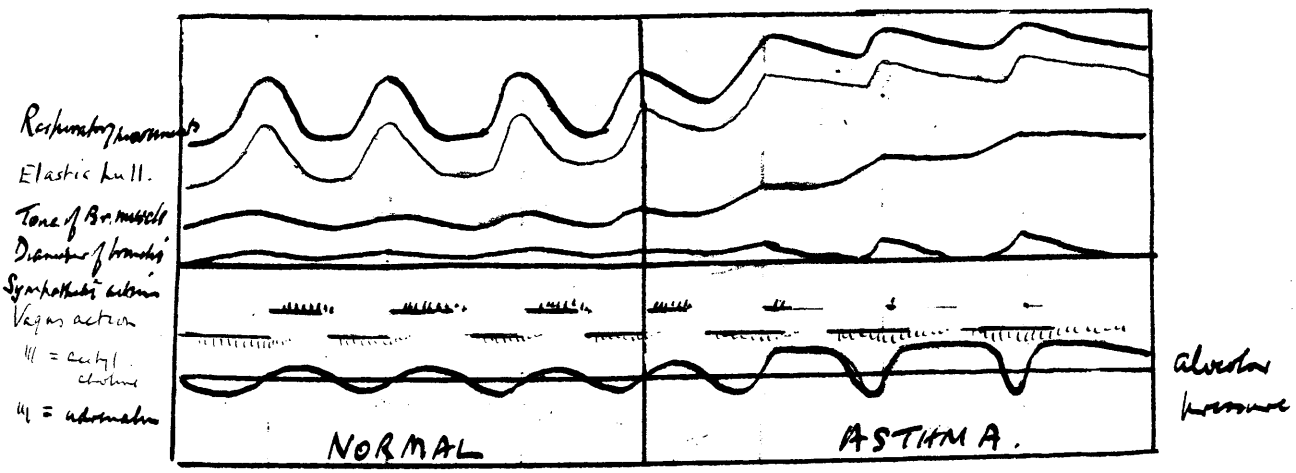
On this view vagus action is designed to prevent undue bronchial dilatation, while sympathetic action is a protection against bronchial collapse. It follows that the defect in asthma is a sympathetic defect. By analogy when we see a patient suffering from internal strabismus we do not at once assume a spasm of the internal rectus, but make a provisional diagnosis of VI nerve paralysis.

HUMORAL THEORY. A good deal of evidence exists that parasympathetic nerves do not produce their effects by direct stimulation of the organs which they supply, but by the liberation of a chemical substance. If a frog's heart is perfused with Ringer's Solution and subjected to repeated vagus stimulation, a substance appears in the perfusion fluid which will produce vagus effects, not only on another heart, but on stomach or intestine. This substance is believed to be acetyl choline.

Similarly sympathetic stimulation sets free a chemical substance which produces an effect like adrenalin, and which may be adrenalin itself. In this connection Burn's work is of interest. He finds that a preparation which has been deprived of adrenalin by washing will not respond to sympathetic stimulation until adrenalin is added to the perfusing fluid.

The importance of the humoral theory lies in this, that the effect of a vagus impulse will continue while the vagus substance is present in the organ supplied, unless inhibited by a sympathetic stimulus. Acetyl choline is an unstable substance and breaks down to the less active choline fairly soon, but a definite time interval must elapse before the vagus effect ceases.

Assuming the truth of what I have stated, I have constructed a diagram of what probably happens.



Asthma may therefore be an achalasia of the bronchi rather than a bronchospasm, though the distinction is perhaps unnecessary.

NB. In the 2nd half of the diagram the alveolar pressure should vary considerably more, but is shown on a reduced scale.

These coordinated actions of the vagus and sympathetic nerves will keep the calibre of the bronchi fairly constant under ordinary conditions, and may be regarded as the normal mechanism.

We find actually that a "wheeze" can be produced by most normal persons on making a forced expiration following a normal expiration. I should explain this by saying that the elastic fibres of the lung were still further relaxed, allowing the bronchial muscle to contract to an abnormal degree. This wheeze can also be produced by breathing out suddenly in the course of a normal inspiration, i.e. before the normal "bronchospasm" has had time to relax. The wheeze can not be produced by a normal person breathing however forcibly if there is a pause following inspiration,* i.e. the bronchial muscle begins to relax at the end of inspiration.

It is commonly stated that in asthma the main difficulty lies in expiration. Asthmatic patients generally do not notice this. They complain of obstruction to inspiration also. If seen between attacks they cannot as a rule carry out full expiration, but rhonchi are noticed towards the end of expiration and the beginning of inspiration, i.e. when the elastic pull of the lung is at its minimum. I think that the reason for the distended chest in an asthmatic attack is simply that in that position the bronchi are subjected to the greatest pull by the elastic tissue. When expiration reaches a certain point the bronchioles collapse as this support is withdrawn, and the phase must cease.

The bronchospasm might theoretically be due to overaction of the vagus or underaction of the sympathetic. There can be very little doubt that the latter reason is the correct one. Adrenalin relieves the attack if given early in doses which are too small to produce a general effect such as pallor, tremor, rise in bloodpressure. This suggests that there is a selective action on the bronchi in asthma.

Burn has shown that the sympathetic nerves require adrenalin to be present before stimulation is effective. I suggest that the asthmatic is producing sympathetic impulses which are ineffective because of the absence of adrenalin from his bronchi. When this is remedied by supplying a minute quantity his bronchi quickly relax.

* At the end of expiration in some cases, this wheeze may still occur

1. Personal Observation.

It is rather surprising that a disease which can be cured by injecting a small quantity of adrenalin should occur at all. As Professor Boycott remarked, "When the body finds itself in trouble it does things which are helpful; this is a law of injury and disease which in its own field is as valid as the law of gravity." The only logical explanation is that the body does not form adrenalin because it cannot.

This theory of physiological bronchospasm is supported by a consideration of the socalled "asthmogenic" areas. It has been shown that stimulation of the ethmoid area may produce bronchospasm even in some normal people, and that the bifurcation of the trachea is also sensitive. The stimulation of those areas by cool air probably plays a part in inducing the bronchial contraction which occurs during inspiration. The warm moist expired air will not produce the same effect.

If we consider an asthmatic at the beginning of his attack, and accept the hypothesis that his sympathetic control is becoming ineffective, it is clear that his bronchi will collapse progressively sooner during each expiratory phase. The lung is now working in the inspiratory position, when lung tension is at its highest. Also the constriction of the bronchioles causes an intrabronchial pressure during inspiration of 50 mm. Hg. These two factors tend to stretch the contracted muscle and reflexly increase vagus activity so that a vicious circle is set up. The increased amount of acetyl choline set free now produces its effect on the mucosa leading to swelling and secretion of the characteristic sputum. It is interesting to note that Harkavy[1] found an alcohol soluble toxic substance in asthmatic sputum which caused contraction of smooth intestinal muscle, i.e. a vagus effect.

The majority of attacks of asthma cease in time without treatment. This natural cure of the attack must be due to a return of sympathetic control as postural muscle is relatively tireless. The effects of the dyspnoea are mainly due to retention of $C.O_2$ and oxygen deficiency. $C.O_2$ increase causes a fall in pH. of blood, with chloride shift and other features of acidaemia. O_2 shortage causes lactic acidaemia, which will increase the fall of pH. The fact that Hb. is a weaker acid than Hb O_2 may partly compensate the acidosis.

1 Bibliography 13

$C.O_2$ causes a constriction of bronchial muscle (Brodie & Dixon), but also causes a free secretion of adrenalin by suprarenals, so that when these organs are physiologically adequate the spasm should quickly subside. The facts that (a) 2 minims of 1/1000 adrenalin will sometimes stop an attack and (b) that $C.O_2$ normally leads to free secretion of adrenalin,[1] are strong evidence that a person in whom an attack of asthma lasts any time must have very inadequate adrenals. The low blood sugar level and low bloodpressure point in the same direction.

The occurrance of asthma as a result of overdistension of the stomach or bowel or of nasal polypi suggests that vagus action may be excessive in these cases. There is another explanation which might fit the facts equally well and will be referred to later. In any case, normal sympathetic control might be expected to prevent such extreme overaction as would cause an asthmatic seizure.

The efficiency of the sympathetic nervous system is known to depend on two endocrine glands, the suprarenals and the thyroids. These both sensitize sympathetic nerve endings, but thyroid action is slower and lasts longer.

The chemical resemblance between adrenalin and thyroxin, both of which appear to be derivatives of tyroxin, together with the fact that thyroxin does not produce an effect for several hours after administration, suggests that thyroxin may be broken down in the body to adrenalin before it can act. Adam describes four cases of asthma in Graves' disease. Osler also refers to the combination but it appears to be rather uncommon, as Mr. MacEwan of Bradford has not seen one example in more than five hundred cases of toxic goitre. The frequency of asthma in this City is considerably more than one in five hundred. The occasional appearance of these anomalous cases may be due to adrenal inhibition, Congestion of the bronchial mucosa from cardiac insufficiency may also be a factor concerned.

McCarrison remarks that cases of Graves' disease are liable to attacks of paroxysmal dyspnoea which are due to weakness of respiratory muscles and thyroid pressure on the trachea, and which may readily be mistaken for asthma. Some cases of Grave's disease show skin pigmentation suggesting adrenal damage.

Oehme and Paul[2] claimed that excess of thyreoid hormone could be demonstrated in the blood in asthmatic attacks using the Reid Hunt technique. If this is the case the thyreoid activity is probably compensatory.

1. Cramer Plate 12
2. Berry p. 105

Although asthma is not found in Addison's disease, the objection to the theory of adrenal inadequacy in asthma is not insuperable. The condition is rare. Gastro-intestinal disturbances occur from the unbalanced action of the vagus, and it may be that asthmatic attacks are so rapidly fatal as to be unrecognised. Death frequently occurs from "syncope" early in the disease.

OTHER EVIDENCE OF SUPRARENAL DEFECT.

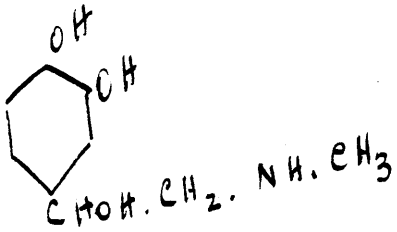
Adam draws attention to the dusky sallow hue of many asthmatics with chloasma round the eyes, "sure token of toxaemia". It is not unreasonable to suggest that this pigmentation may equally be due to depression of suprarenal function. A similar appearance may be noticed in some women at the menstrual periods, when a "vagotonia" occurs.

A large number of asthmatics show an ocular sensitivity to adrenalin which is not found in the normal person. The pupil of an asthmatic is unstable. In a bad light it may be seen to contract and dilate more or less in time with the respiratory movements. The instillation of adrenalin increases the hippus and quickens the rhythm.[1] In a number of male asthmatics a contraction of the pupil was also noticed. This sign was not elicited in any of the females tested.

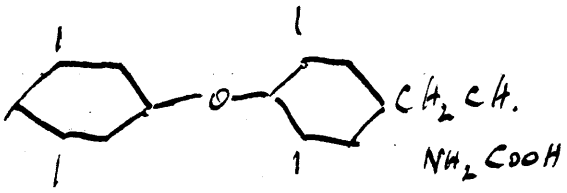
As Coke points out, "Most of these patients are blessed with wonderfully pleasant, even jovial, dispositions which stand them in good stead." If we accept Cannon's view that anger causes suprarenal secretion, the inference from this is that asthmatic patients do not secrete adrenalin as readily as normal persons, which is in accordance with the conclusions reached on other grounds.

The association between overheating and suprarenal inhibition is illustrated by the pigmentation of the skin of the legs, commonly met with in those who sit for long periods close to a fire - the "erythema ab igne". It may be that this condition is analogous to the melanin deposits in the skin in Addison's disease. The site of the pigmentation depends on local causes, but there is no doubt a systemic change also - due to adrenal inhibition.

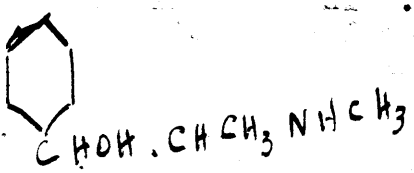
1 Personal Observation.



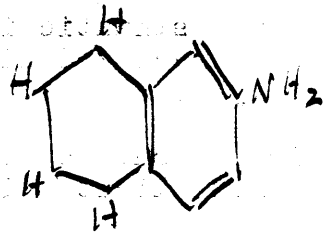
Adrenalin



Thyroxin.



Ephedrine



β tetra hydronaphthylamine.
(T.H.N.)

Graphic formulae of Sympathetic stimulants

THYROID ADRENAL APPARATUS.

The influences affecting the activity of the thyroid and suprarenal gland can best be understood by consideration of the normal function of the sympathetic nervous system. Sympathetic stimulation increases heat production by augmenting katabolic processes, and diminishes heat loss by constriction of peripheral blood vessels, thus bringing about a rise of temperature. Sweating and erection of hair are also caused which tend to favour heat loss, but the importance of these is reduced by the peripheral vasoconstriction.

Fever can be produced by strong stimulation of the sympathetic. A hectic type of fever can be caused by excessive thyroid feeding. A hyperpyrexia is produced by β tetra-hydro-naphthylamine (T.H.N.) which causes extreme adrenal activity. 1

Cramer regards the sympathetic nervous system as the heat regulating mechanism of the body, and considers that the rise of temperature following bacterial invasion is due to stimulation of thyroid and adrenals. This view is supported by much clinical evidence. The low temperature of severe diphtheria and the subsequent debility are thus explained, as the suprarenals are known to be damaged in this disease. The postinfluenzal debility is due to the same cause. It is worthy of note that those fevers which are followed by marked debility (evidence of suprarenal damage) are those which are frequently followed by bronchitis or bronchopneumonia. I refer to diphtheria, measles, whooping cough and influenza, which are frequently given by patients as starting points for asthma. The pigmentation of the skin in measles convalescents is probably analagous to that of Addison's disease.

The toxins of B. diphtheriae and B. Welchii are those which have been shown experimentally to produce adrenal exhaustion. In both cases the cortical lipoid is greatly reduced. B. Welchii causes almost complete disappearance of lipoid (Cramer plate 32). Whether this action of B. Welchii has any significance in the causation of asthma is uncertain.

Using a special histochemical method Cramer has been able to demonstrate adrenalin granules passing into the adrenal veins as a result of exposure to cold, T.H.N. injection, or streptococcal infection.

1 Cramer. See also Appendix a)

Similar changes occur in the thyroid though taking longer to appear. Mice which had been fed on thyroid until their alveoli were full of colloid, showed great diminution of colloid after three hours in a cold room (4°C). On the other hand a warm environment causes accumulation of colloid. Seasonal variations in the iodine content of the thyroid have been observed repeatedly. It is higher in the Summer than in the Winter.

Now the factors inhibiting adrenal activity are those with which we are mainly concerned. A physiological inhibition must occur in health, as adrenalin stimulates sympathetic nerves and sympathetic activity stimulates adrenalin secretion, so that a vicious circle might be readily established in the absence of some check. Cramer has shown that the presence of a moderately large amount of adrenalin in the blood causes certain changes which he describes as "self control" of the adrenal. In this condition adrenalin disappears from the peripheral part of the medulla. Cramer considers that the precursor of adrenalin is formed in the cortex and that adrenalin itself is chiefly formed in the outer medulla, so that apparently the presence of a certain amount of adrenalin in the adrenal artery inhibits the formation of the hormone. The condition is also found after thyroid feeding in small doses over a long period. Large doses may stimulate the adrenals for a short time.

Exposure to heat causes changes of a different type. The cortical lipoid disappears from the zona fasciculata, and is found in reduced amount in the outer part of the zona glomerulosa. These experiments were carried out on rats and mice whose reaction to heat is impaired by the absence of sweat glands except in the pads of the feet, and may not be applicable to man to the same degree, though something of a similar nature probably occurs.

Cramer's view of the interrelationship of cortex and medulla conflicts with the accepted one, but it must be obvious that the blood supply will cause the medulla to be influenced by cortical activity. The arterial supply enters the cortex and the blood passes through both parts before reaching the central vein. The association of cortical changes with medullary activity is strong evidence bearing

out this view. The amount of cortical lipoid present is taken to be a good indication of the degree of activity of the medulla.

We have seen that the suprarenal medulla is inhibited by certain bacterial toxins, by heat and by excess of thyroid substance in the body, i.e. thyroid in excess of metabolic needs. This enables us to understand the origin of the hypoadrenalinaemia which we have deduced to be present in asthma.

A. It may be due to an acute infection such as diphtheria, measles, pertussis, influenza or pneumonia, and may be temporary or permanent.

B. It may be due to insufficient stimulation of the heat producing apparatus of the body, e.g. by indoor habit with lack of exercise, living in warm rooms, overclothing and general coddling. This regime frequently follows the acute infections described, and may convert a temporary adrenal inadequacy into a permanent one.

C. High carbohydrate diet by maintaining a high blood-sugar level will lessen the demand for sugar production by the liver. This demand is conveyed by adrenal activity, so that high blood sugar produces inactive adrenals.

It is a common experience that asthmatics wear too much, keep themselves warm, avoid exercise, and frequently eat starchy food to excess. They often remark that a warm room makes their breathing difficult, but do not apply the fact to the alteration of their regime.

The relative importance of thyroid and adrenal activity may be estimated by consideration of the points in which their secretions differ pharmacologically. Adrenalin acts quickly and is quickly destroyed. Thyroxin acts more slowly, but produces a more lasting effect. This suggests that adrenalin is secreted to produce small variations in metabolism, while thyroid activity fixes the general level.

We know that asthmatics have a subnormal basal metabolism. and that the conditions of the life they generally lead do not produce marked variations in the metabolic rate. The chronic

bronchitic generally reduces the area of his skin which is radiating heat to the minimum, so that changes in external temperature do not affect his metabolic processes to the normal extent. His liking for warm clothing and many blankets reduces his basal calory requirements. These peculiarities may be due, and no doubt are due in some cases, to a primary failure in heat production, but by reducing the need for internal heating they must cause an accentuation of the condition.

ASTHMA IN INFANTS.

The child who has bronchitis or broncho-pneumonia during dentition is likely to develop asthma in later years. The conditions giving rise to the bronchitis are similar to those causing asthma. Living in warm rooms, overclothing and "slop feeding" (Adam) are potent causes. The association with dentition is presumably due to reflex vagal stimulation.

The excessive incidence of the disease in artificially fed children may be explained by the fact that human milk contains thyroid secretion, while cow's milk does not (McCarrison). As the human thyroid at birth contains little or no iodine it follows that the artificially fed infant will be subthyroidic until a mixed diet is adopted. A child breastfed by a subthyroidic mother is in more or less the same position.

In these young children undue congestion of the bronchial mucosa is of more frequent occurrence than bronchospasm. The nervous mechanism appears to be the same in each case, but the congested mucous surface is readily invaded by organisms and a true inflammatory condition results.

Prophylaxis (Parsons & Barling)[1] consists in acclimatising the child to cold by exposing it out of doors for increasing periods, to which may be added the administration of small doses of thyroid extract.

1 Diseases of Infancy and Childhood 1933 p. 914

The so called "pneumonia jacket" for these children is aptly named. The common overheating of the sickroom and use of a steam tent are equally objectionable, at least in afebrile cases. I have frequently seen a "bronchial" child remarkably improved by simply removing excessive clothing, allowing the child to run about indoors, giving small doses of thyroid extract, and cutting down the milk allowance. Coke advocates open air treatment for these cases of recurrent afebrile bronchitis, with which I agree heartily.

In this connection it is of interest to note Leonard Hill's recent work on the effect of infrared radiation on the nasal mucosa.[1] He finds that the long infrared rays which heat the skin without causing vasodilatation (i.e. reduce heat loss) cause congestion of nasal mucous membrane. This may be prevented by cooling the face or other part of the body. The nervous mechanism involved is not clear, but it is not unreasonable to suppose that the reduction in heat loss causes a reflex inhibition of the sympathetic system generally, and that the nasal congestion is only one manifestation of a general vagotonia. In any case, undue heating by infrared rays undoubtedly increases liability to rhinitis and respiratory infections generally. The logical method of avoiding these infections is to stimulate metabolism by occasional chilling.

1. Bibliography 14, 15

HEREDITY IN ASTHMA.

The tendency for asthma to be a family disease may arise in three ways.

A. There may be an inborn defect of the sympathetic nervous system, or of that part of the system which innervates the bronchi.

B. The breast-fed children of subthyroidic mothers will receive less than the normal amount of thyroid substance during the period of lactation, which may dispose towards bronchitis in infancy. When one attack has occurred the child's doom is sealed. He is henceforward wrapped up and coddled so that his chance of developing his heat producing mechanism is greatly reduced. This applies to an even greater extent where the child is artificially fed, which is a tradition in some families.

C. The clothing and feeding of children are often governed by family tradition, which is not weakened by the bad results obtained in previous generations. As Adam points out, it is difficult to cure a child of asthma if it has two grannies and several aunts. Some of my asthmatic patients are very critical of the lack of care displayed by parents who allow their children to go out with "insufficient" clothing and to sleep in cool rooms. They themselves were not brought up like that - hence their asthma.

TREATMENT:

This should be directed to stimulating sympathetic activity generally.

1. Exposure to cold. Wearing apparel should be reduced to the point at which the patient feels chilly. A cold shower in the morning followed by exercises for ten minutes in the nude with the window open is helpful. Cold sponging of face and hands several times daily may be advised.

2. Exercise ought to be taken daily in the open or in a cold room with a minimum of clothing.

3. Ephedrine should be given in small doses over a period to assist the change of habits by stimulating sympathetic activity.

4. Thyroid substance should be given for a short time until the patient's own thyroid can be trusted to supply the increased amount required.

5. Diet should be high in protein for specific dynamic action and low in carbohydrate for stimulation of glycogenic function. Milk should be cut out of the diet, as it is known to depress thyroid activity.[1] It is generally stated by asthmatics that milk "clogs" their breathing. This applies to sensitive and non-sensitive asthmatics equally. Fats should be restricted as they are thyroid antagonists.

There is often difficulty in getting this programme carried out. Asthmatics are obsessed with the fear of catching cold. Where there is real susceptibility to respiratory infection a Vitamin A preparation is useful. They often feel the cold badly as their suprarenals are unaccustomed to react to it. Ephedrine and thyreoid tide them over this period. These two drugs have a much better effect given together than separately, because the sympathetic stimulation of the ephedrine makes the patient capable of utilising the thyroid supplied.

1 McCarrison Brit. Med. J. 14.10.33 p. 671. See also Appendix (C).

To give small doses of thyreoid (less than 14 mgrms. thyroxine daily) (Kendall) without increasing the metabolic call for it is useless, as the patient's own gland reduces its contribution by a similar amount and stores colloid.[1] This explains the general failure in the use of thyreoid medication for asthma and other conditions. This remark does not of course apply to myxoedema where storage capacity is often absent - hence the poor thyreoid tolerance in this disease.

I give to an adult 3 - 5 grains thyreoid* in the morning with ¼ gr. ephedrine at night. The results seem to be better than with ½ grain doses of ephedrine given alone. The thyreoid ephedrine treatment should be stopped when the patient's metabolism has been brought to a normal level, as estimated by tolerance of cold, and exercise taken.

This combination is particularly useful in the treatment of obesity.

The tendency to bronchial spasm and catarrh following acute infections can be combated by giving thyreoid alone, as the condition is probably due to exhaustion of colloid reserve.

The efficacy of Knott's thyromanganese "detoxication" treatment in some chronic conditions probably depends on a similar action. Manganese pharmacology is rather obscure. Von Jaksch states that manganese poisoning is associated with impulsive laughing and impulsive crying, suggesting sympathetic stimulation.

It is interesting to consider other methods of treatment in the light of the theories here described.

a. Atropine and Belladonna act on vagus nerve endings. They may be of service in non-sensitive asthmatics, but of less value in sensitive. As Besredka found, atropine does not prevent anaphylaxis, which acts beyond the nerve ending.

b. Potassium Iodide which is supposed to act by diluting the bronchial secretion may act by stimulating thyreoid function. Rendle Short found that thyreoid substance could replace K.I. in treating tertiary syphilis.[2]

* B.P.1914 Thyreoid Extract is referred to throughout.

1 Storage of colloid in thyroid gland – See Cramer pp 41 46.
2. Rendle Short, "New Physiology in Surgical & General Practice". Quoted by Gabriel Cobb.

c. Chloroform in an attack causes adrenalinaemia.

d. Morphine. A number of fatal cases have been described. The drug should not be used.

e. Coffee (or caffein) is sometimes helpful. The alkaloid is said to act on the vasomotor centre raising the blood-pressure, i.e. acting on sympathetic nerve endings.

f. Mixed Coliform Vaccine (Danysz).[1] McCarrison holds that organisms whose normal habitat is the intestine have a profound effect on the thyreoid gland. B. coli injection is found to cause a rise in blood sugar, i.e. it is a sympathetic stimulant.[2]

g. Peptone will exert the "specific dynamic action" of protein.

h. Nasal treatment - Dowling packs etc. by reducing sensitivity of mucous membrane may diminish vagal activity. It is generally admitted that nasal treatment alone will produce very little benefit. On the other hand, good hygiene will improve the nasal condition. Coke describes a case where polypi were cured by general measures.[3]

i. Calcium preparations. As calcium diminishes thyreoid activity (McCarrison), it might be expected that calcium therapy would do no good in asthma. This appears to be true.

j. Elimination (Hazeltine and La Forge). Free purgation with mercurials and great intake of fluid by mouth are main features of this system. McCarrison advises mercury in subthyroidism, attributing its efficiency to an intestinal antiseptic action. He quotes Sajous, however, as regarding Hg. as a thyreoid stimulant. Part of the benefit derived from this treatment may be due to heat loss.

1 Recommended by Coke.

2 Cramer p. 121

3 Coke p. 245

k. Glucose is used by some as an adjuvant. By increasing the level of the bloodsugar glucose will lessen suprarenal stimulation. In the absence of liver disease the glycogenic function[1] will respond to other measures previously described. Glucose treatment is claimed to produce improvement in 30% only of cases even in children, and the proportion is smaller in adults. The advisability of giving glucose in free intervals is very doubtful as stimulation of hepatic function (glycogenesis) is reduced.

l. Bowel washouts (Cameron). In this form of treatment large quantities of water at body temperature are used for colonic lavage. By diluting colonic contents this method may favour absorption of coliform toxins and so stimulate the sympathetic system. If the temperature of the water has fallen by the end of the treatment heat loss will also act.

m. High altitude. As Hurst points out, asthma is cured by residence at 4,000 ft. Going much higher may cause a return of asthma. The usual explanation of allergen-free air is unconvincing. The interior of the Swiss chalet, often badly ventilated, must be full of allergic material. Mansfield and Muller have found that anoxaemia stimulates thyreoid function, which is a more likely explanation.

n. Morley Agar treats the ears, face and scalp with a lotion composed of carbolic acid, ol. menth. pip. and spirit which he claims to be beneficial. This treatment by producing hyperaemia of the exposed parts will increase heat loss.

1 The term is used in the sense originally suggested by Claude Bernard. For a short account of the glycogenic as opposed to the storage hypothesis of liver function see Cramer h. Do.

2 Brain. h 240

CLINICAL CASES.

Case 1. Cecil Stead, aet. 36 yrs. Army pensioner.

Family History: Father died of phthisis and his mother of bronchitis.

Medical History: This man was fairly healthy before his War service. He sustained a severe facial wound in 1918. Subsequently he developed respiratory trouble which was diagnosed as phthisis in 1920. This diagnosis was almost certainly mistaken. At any rate, there is no evidence of present tuberculosis. Since 1920 he has had many attacks of asthma, mainly nocturnal, and before coming under treatment averaged three a week. His longest period of freedom from attacks during the last three years occurred while he was at Scarborough in August 1933. He was free for 14 days.

This man had a septal resection in 1931 which did not benefit his asthma. Before this operation he had two injections of haemoplastin as he was said to bleed easily. Following these injections he developed a chronic urticaria which was very intractable and has also had several attacks of angioneurotic oedema affecting the face and neck.

Ephedrine gr.½ night and morning in June 1933 gave some relief but not freedom.

Physical Examination: Height 5'7", weight 11 st. 8 lbs. When the patient was first seen there were many adventitious sounds in the chest, but percussion note normal or hyperresonant. Some emphysema was present. The heart was not enlarged. Blood pressure 120-85 and arteries healthy. The skin showed some urticaria, but negative response was obtained to all proteins tested.

The patient was rather obese and absurdly overclothed. He volunteered the information that he could not stand too hot an atmosphere. His clothing was not only generally excessive, but he wore a chest-protector and a thick woollen scarf habitually.

Treatment: On 30th October, 1933, I prescribed him thyreoid gr. 5 to be taken in the morning and ephedrine hydrochloride gr. ¼ at night. He was also advised to reduce his clothing to the minimum consistent with comfort, to avoid milk and to obtain regular outdoor exercise. He has had no attack since (Dec. 31st, 1933) though he still has a few rhonchi occasionally. His exercise tolerance is greatly improved, and his weight is reduced by 10 lbs. He has recently had a return of skin trouble. The skin is dry, hyperaemic and irritable, with dermographia.

Case 2. Mrs. Harriet Brewer, aet. 50 yrs. Housewife.

Family History: Her father had "bronchitis" also her mother. She has one sister who is well, and has only had one child who died of pneumonia at the age of twelve months.

Medical History: Asthma since the age of twenty. Worse in the last ten years. She associates attacks with chills, fog or smoke. She used to be better in the summer, but not during the last two years. Average frequency of attacks - two a week, nocturnal in type. Exercise tolerance extremely poor.

Physical Examination: Height 5'7", weight 13 st. 9 lbs. Bronchitis and emphysema. Blood pressure 120-80, the arteries were healthy, skin dry (always has had a dry skin[1]) and chloasma present round the eyes. Four years amenorrhoea. Clothing definitely excessive. Indoor life mainly in a warm kitchen, and keeps chest and throat covered for fear of a chill.

1. Except at "change of life" when she had sweating attacks.

Treatment: In September I commenced giving her thyreoid gr. 5 and ephedrine gr. ¼ once daily. She was also persuaded to reduce her clothing and to expose the neck and upper part of the chest. She always has avoided milk as her own experience has made it clear that milk precipitates attacks. Since the treatment was instituted she has not had one attack. There is still a little bronchitis, but orthopnoea has disappeared, and exercise tolerance is greatly improved. Incidentally this is the first November for six years during which the patient has not had to remain in bed. Weight has been reduced to 12 St. 2 lbs., i.e. a loss of 21 lbs. Her skin is now dry and hyperaemic, but does not cause any subjective symptoms.

Case 3. Mrs. Lily Brown, aet. 44 yrs. Housewife.

Although this patient has not been treated on the lines I have described her case is of interest in other directions.

Family History: Mother chronic bronchitic, father epileptic. One sister and brother both have petit mal. Another sister is obese and subthyroidic, improving under thyreoid treatment. The patient herself displays an unusually complete association of so-called allergic diseases.

Medical History: Asthma for fifteen years, epilepsy for about the same time. She has suffered from psoriasis, mainly in the Spring, for many years. She is always anaemic and obese. Her asthma is less troublesome during pregnancy. During her tenth pregnancy which terminated on October 31st, 1933, she had one attack only, which was relieved by ephedrine gr. ½. An easy natural labour was followed by extreme collapse not due to excessive blood loss. The pulse rose to 180 and later became imperceptable. Blood pressure was 70-60 at one time, but later could not be determined. I administered 1000 c.c. of gum

saline with 1 c.c. of coramine added into the median basilic vein. 30 minims of adrenalin 1/1000 were added to the intravenous infusion, a drop at a time, with considerable benefit.

This alarming collapse was not due to excessive haemorrhage and to my mind indicates a hypo-function of the vasomotor mechanism, i.e. the sympathetic nervous system.

During convalescence I gave her ephedrine gr.½ daily to maintain vasomotor control and gave intensive treatment with intramuscular liver and drachm ½ Ferri et Ammon. Cit. t.d.s. Her haemoglobin percentage is now 60.

Physical Examination: Height 5'4", weight was 12 st.,now 10 st. 5 lbs. Blood pressure 110-80, arteries sound, some chronic laryngitis, skin dry, hair poor in texture and scanty. Hertoghe's eyebrow sign present. Anaemia, Wassermann negative. This patient is not so excessively clothed as some, but wears more than normal amount.

Treatment: This patient's epilepsy is controlled by luminal gr. 1 daily. As mentioned above she had ephedrine during her last puerperium. Since then she has had thyreoid gr. 1 t.d.s. with considerable improvement in her general health. Her weight is reduced to 10 stone, and she has had no attack of asthma since. I do not claim that her asthma is cured, as her freedom during pregnancy was due to her physiological condition, and her present freedom from attacks may be of a similar nature.

I regard this particular case as one of myxoedema, of a mild type.

Case 4. John T. aet. 3 yrs.

Family History: Paternal grandfather was a life long asthmatic. There is also history of bronchitis on the mother's side. The patient's sister is well.

Medical History: Bronchitis during dentition. Two febrile illnesses suggesting broncho-pneumonia but clearing up quickly. Definite asthma commenced December 1932, mainly nocturnal, though there was a good deal of wheezing during the day also. This child had had chloral and bromide, peptone before meals, and ephedrine at night with slight benefit. Eczema was present in early infancy and during dentition.

Physical Examination: Rather adipose pale child with generalised rhonchi. Skin dry, rather too well clothed, indoor habit. This child was inactive and spent too much of his time in warm rooms. The skin was sensitive to egg only among the proteins tested.

Treatment:

Daily exercise in a cold room, wearing nothing above the waist was adopted. Thyeroid gr.1 and ephedrine gr.$\frac{1}{4}$ (later gr.$\frac{1}{8}$) were given, and restriction of milk advised. This regime reduced the asthma very considerably. In the two months following institution of treatment only one nocturnal attack occurred. This was associated with constipation and during the two days previous the child had missed his exercise and his ephedrine. Unfortunately this patient has an unusual liability to catarrhal infections, and has recently had a mild attack of asthma following coryza. Adexolin has been advised to correct this tendency.

Since the treatment was started growth has been more rapid, and the child is now much more active. The only disadvantage of the ephedrine treatment has been a tendency to

nocturnal excitement. This has occurred on three or four occasions, and is no doubt due to the dose being too large.

I attribute the asthma in this patient definitely to overheating by clothing and warm surroundings combined with hereditary tendency and "slop diet". The child had an aversion to meat, and his protein intake was small. Incidentally he has been allowed to have eggs which do not influence his asthma one way or the other.

5.1.34 This child is now perfectly well. No wheezing whatever at all. Has had no medicinal treatment for 5 or 6 weeks.

Case 5. Billy Sugden, aet. 3½ yrs.

Family History: Mother obese and subject to bronchitis.

Medical History: In October this child had an attack of measles. The rash appeared on the 27th. On October 31st his chest was full of adventitious sounds and the breathing was difficult. He had then been in bed five days in a warm room on a milk diet. I told the mother to let him get up and play about indoors, to give him ordinary diet and not wrap him up. He was also given thyreoid gr. 2 daily. On 3rd November his chest was perfectly clear, breathing was quite normal and the child was well and sound. I have no doubt from experience of similar cases that a continuance of milk and bed would have prolonged his bronchitis a week or more.

Case 6. Baby Benson, aet. six months.

Family History: Three other children all had bronchitis in infancy.

Medical History: This child was seen on the 22nd November. There was generalised bronchitis and considerable dyspnoea. Temperature was normal. The child was in a warm kitchen and was shockingly over-

clothed. In addition to many woollen garments and blankets he was wearing a "pneumonia jacket" which had been supplied by the local Infant Welfare Clinic. His mother had been told that this must on no account be removed. The first step in the treatment was to reduce the clothing by 50 per cent and discard the pneumonia jacket. He was also given thyreoid gr.½ daily. On the 25th November he was perfectly normal, three days afterwards. It turned out that this child's life was mainly spent in the kitchen. He was rarely taken out. The room temperature was nearer 80°F. than 70°F., yet he was clothed in a manner suitable for Arctic conditions.

Case 7. Rose Mary Handley, aet. 4 yrs.

During 1931 and 1932 this child was rarely free from bronchitis. She also had two attacks of bronchopneumonia, and on several occasions had definite dyspnoea of an asthmatic nature. A tonsil and adenoid operation produced no improvement. This child lived in the kitchen which was without exception the warmest room I have ever known. I explained to the parents that the bronchitis was directly due to overheating, but the child's grandfather (also a bronchitic) would not allow any change to be made. In December 1932 he died. Since then the room has been kept at a reasonable temperature, and the child has had no bronchitis, although diet and other factors have remained unaltered.

Case 8. John Crossley, aet. 2 yrs.

In 1931 this child had very severe bronchitis. There was a suspicion of tuberculosis, and the child was seen by the Tuberculosis Officer who advised codliver oil and malt and wrapping up. The mother was a careless woman and neglected the child. I have seen him running outside on a

cold winter day wearing only a shirt. His bronchitis improved and he made a spontaneous recovery. This case was one of several which suggested to me the definite association of overheating and bronchitis.

Case 9. Phillip Kelly, aet. 6 yrs.

Seen in March 1932 suffering from afebrile bronchitis. He was said to have had bronchitis all his life, had had two attacks of broncho-pneumonia, and was frequently away from school. Tonsils and adenoids were present. The treatment previously adopted had been to wrap him up in thick woollen undergarments, put him to bed when an attack started and poultice his chest. I advised minimum clothing and plenty of out-door exercise irrespective of the weather. As there was a tendency to catarrhal infection I gave him one Adexolin capsule daily for a month. He has had no bronchitis since. His tonsils and adenoids were removed during the following autumn, which measure reduced the tendency to coryza.

Case 10. Baby Jordan, aet. three months.

In October 1933 seen with bronchitis, afebrile. Mother cannot understand it as "the child has not been outside for a week". The kitchen was very hot. The mother was advised to take the child outside, and gr. ½ thyreoidi given daily for four days as a precautionery measure. The bronchitis cleared up immediately.

Case 11. Mrs. Harrison, aet. 47 yrs. Housewife.

Family History: This patient's sister suffers from chronic bronchitis and her father suffered from asthma.

Medical History: She herself has been subject to asthma as long as she can remember. Her attacks are relatively infrequent, occurring perhaps twice or three times in the year. She wears rather less than the usual amount of clothing, and leaves the throat and manubrium sterni exposed even in the coldest weather. She has found from her own experience that covering these parts renders her liable to an attack. She also finds that remaining indoors for several days brings on an attack. In October 1931, on the advice of her friends, she obtained some thick woollen underwear and a woollen scarf with the intention of avoiding chills. However, she had the worst Winter she can remember. Since then she has put up with feeling cold and has remained comparatively free. She avoids milk, having found that it upsets her.

Physical Examination: When seen nothing of note was made out. She is rather overweight. Heart and arteries are sound. Skin is rather dry. Chest clear when seen.

Treatment: As the attacks are so infrequent she was advised to continue on her own lines which would be difficult to improve upon. This lady is one of the most sensible asthmatics I have met, as she can apply her own observations in spite of their conflicting with her training and popular opinion.

However, she consulted me in November complaining of debility following a catarrhal infection. I prescribed thyreoid gr.1 t.d.s. and the clinical improvement has been so remarkable that I intend to try the effect of continuing thyreoid treatment. The patient states that she feels better than she has done for many months. There are no clinical indications of subthyroidism with the exception of moderate obesity.

Case 12. Moses Nichol, aet. 52 yrs. Woolcomber.

Family History: Patient could give very little information except that his father had bronchitis.

Medical History: Patient had no bronchitis till the age of 35. Until that time he was interested in athletic pursuits, but following the cessation of these activities he put on weight and began to be troubled with "bronchitis", which is actually bronchial asthma. The attacks have occurred mainly during the Winter months, and have been mainly diurnal. Patient is a night worker. Previous treatment consisted chiefly of prescription of expectorant mixtures and the attacks occurred frequently with severe dyspnoea and orthopnoea.

The only other illness of note was an attack of lichen ruber planus in December 1930. An unusual feature of the condition was the total absence of pruritus. The diagnosis was confirmed by Dr. Eurich of Bradford, and the disease ran the typical course.

Physical Examination: 23.10.33. Height 5'4", weight 14 st. Bronchitis and emphysema. Blood pressure 155-90. Heart and arteries appeared sound but exercise tolerance very poor. The skin was dry and the mucous membrane was rather pale. Wassermann Reaction was negative, and the urine contained no abnormal constituents. Clothing very excessive. This man works as a woolcomber where the average temperature, even in the Winter, is over 90°F. In spite of this he wore considerably more than the averggge outside worker - to avoid a chill.

When I saw him at home he was sitting over the fire in an uncomfortably warm room wearing clothing suitable for outdoor use plus a thick woollen muffler. He was afebrile.

Treatment: I have persuaded him to reduce his clothing though even now it is excessive. He was advised to stop his glass of milk at bedtime and take black coffee instead. He was given gr.5 of thyreoid and gr.¼ of ephedrine daily and an expectorant mixture. The result of these measures

has been that he has been free from acute dyspnoea since treatment started, his exercise tolerance has improved and that his weight has come down to 12 st.10 lbs.

This man shows particularly well the effect of undue diminution of heat loss. It is a curious fact that his wife is also an asthmatic. She has very infrequent attacks, mainly following catarrhal infections. She wears normal clothing with the fashionable low neck dress. When I commented on this she said that she dare not wrap her throat up or she would have an attack, but her husband does not appear to have applied this to his own case.

Case 13. William Mo Avan, aet. 23 yrs. Woolcomber.

Family History: Several members of the family are said to suffer from bronchitis.

Medical History: With the exception of the infectious diseases of childhood he was well till the age of 11 yrs. when he suffered from an attack of pneumonia attributed to being wet through for a period of some hours (probably correctly attributed to this). Since that time he has had frequent attacks of afebrile bronchitis with nocturnal dyspnoea, i.e. asthma. He had had expectorant mixtures.

Physical Examination: Height 5'6", weight 9 st.10 lbs. This young man was well developed and muscular without excessive adipose tissue. Skin is normal, and there is no history of skin disease. Heart and arteries presented no apparent abnormality. Slight emphysema. There was definite turbinate enlargement. Patient is a heavy cigarette smoker. He wears rather more clothing than is quite necessary, especially in view of the warm nature of his occupation. He plays football once a week in the season, but otherwise gets no outdoor exercise.

Treatment: He was advised to reduce clothing, increase exercise, and cut out milk from his diet. This latter advice was unnecessary, as he had already done so having found that it "stuffed his chest". He was also given thyreoid gr.2 and ephedrine gr.¼ daily. Since that date (Nov.11th, 1933) he has had no dyspnoea. This is unprecedented over a period as long as two months, since his illness commenced. He still complains of an irritable cough which I attribute to cigarette smoking.

Case 14. William P. Patrick, aet. 44 yrs. Labourer.

Medical History: This man's asthma commenced in 1917 following a chest wound in the War. The bullet did not enter the thoracic cavity but damaged the chest wall. His asthma commenced in a Convalescent Home where, as he says, he was being built up. He has it Winter and Summer, and is worse when he gets a cold. Attacks are nocturnal. He occasionally has dyspepsia.

Physical Examination: Height 5'7", weight 10 st. This man is well-developed and muscular, without excessive adipose tissue. His heart and arteries are sound. Blood pressure 120-85. Skin normal; no history of skin disease. Iris is very unstable in a dim light. The application of adrenalin to the right eye caused an apparent constriction of the pupil with definite hyppus, an appearance which was also obtained in cases 12 and 13. Clothing normal in amount. He volunteers the information that he is worse in a hot room.

Treatment: He was given thyreoid gr.3 and ephedrine gr.¼ on 30.10.33. Since that date he has had no asthma though he still complains of an irritating cough.

Case 15. Sarah Tomkinson, aet. 58 yrs. Weaver.

Family History: Father suffered from bronchitis, one brother was a chronic asthmatic and died of "chest trouble".

Medical History: This patient has had asthma occasionally for many years, becoming worse during the last five years. She had an operation for genu valgum in October 1932 and is unable to take much exercise. Attacks are mainly nocturnal, but she was rarely free from wheeze.

Physical Examination: A stout lady with general bronchitis and emphysema. Some arteriosclerosis and a doubtful myocardium. Clothing excessive. Indoor habit.

Treatment: In October 1933 my partner, Dr. Trewick, who looks after this patient, advised frequent bowel washouts. At my suggestion he also prescribed thyreoid gr.5 and ephedrine gr.½ daily. Since that time she has had no asthma, and when last seen (18.12.33) had no wheeze. She says that she has been better this Winter than at any time in the last five years.

Case 16. Caroline Tomlinson, aet. 32 yrs. Machine Minder.

Family History: Rest of the family healthy.

Medical History: Asthma since childhood. Pneumonia three times. Measles pertussis. Asthma always in the Winter, mainly nocturnal, worse before and during katamenia. Although she says that the asthma is worse in the Winter time, she finds that she is better in the cold than in a warm room. Wears sensible clothing with low neck and "can't do with anything round her neck". She does not take milk as it "clogs" her chest.

Physical Examination: Height 5'4"; weight 8 st.2 lbs. Bronchitis and emphysema. Heart and arteries apparently sound. Blood pressure 110-60. Skin rather dry; hair poor in texture. No history of skin disease. Clothing sensible.

Treatment: This patient was given thyreoid and ephedrine, but sufficient time has not elapsed to enable one to conclude that improvement is due to treatment. The case is quoted to show harmful action of overclothing and milk diet in asthma.

Case 17. Joseph Holdsworth, aet. 67 yrs. Dyer's Labourer.

Medical History: "Bronchitis" for last fifteen years, mainly in Winter months. The attacks are chiefly nocturnal with orthopnoea, but there is also much bronchitis during the day. His last attack began within a day or two of resuming the use of an eiderdown quilt which was the only alteration in his regime that I could discover. However, skin tests were negative to goose, duck and hen feathers, and I was forced to the conclusion that the influence of the quilt, if any, was due to diminution of heat loss.

Physical Examination: Height 5'7"; weight 9 st. 7 lbs. Chronic bronchitis and emphysema. Arteriosclerosis. Skin dry and thin, unusually translucent. Clothing excessive.

Treatment: Until this year he had most relief from a mixture containing Lobelia and Ammon. Carb. Ephedrine was tried in 1931 with little benefit. At the beginning of October this year I gave him drachm doses of an alkaline powder (Calcium phosphate 2 parts, Magnesium Carbonate, Sodium Citrate aa. 1 part) with marked benefit, so much so that he did not consult me again for six weeks. On November 20th I started him on thyreoid gr.3 and ephedrine gr.$\frac{1}{4}$. He had no nocturnal attacks

Case 18. Matthew Keenan, aet. 20 yrs. Bobbin Pegger.

Medical History: Bronchitis from infancy. Diagnosis of asthma made in 1929. His tonsils and adenoids were removed in November 1929 with temporary improvement. In October 1929 he had turbinotomy done. In spite of these measures asthma continued. In November 1933 he was averaging two moderate attacks a week, and occasionally had a severe attack lasting three days. Treatment consisted of lobelia, pot. iod., and expectorants.
He has not been to work since November 1929.

Family History:
Patient's parents and brothers are well. He says that all his father's people had bronchitis and are now dead.

Physical Examination: Height 5'5"; weight 9 stone.
Rales and rhonchi and some emphysema (3.11.33).
Chronic nasal catarrh. Dry skin.
Clothing excessive.

Treatment: Advised reduction of clothing, daily outdoor exercise. Prescribed thyreoid gr.3 and ephedrine gr.$\frac{1}{4}$ daily. He had no attack from this date until December 30th when he felt rather wheezy on first waking in the morning. This soon passed off on going outside. I have told him to look out for a job.

during the next fortnight, but the treatment had to be stopped on account of insomnia. He is now receiving the alkaline powder again, and is satisfied that the results are good. The rationale of the treatment is based on Adam's opinion that asthma is associated with an acidosis, and by giving an adequate supply of mineral bases the body is assisted in maintaining a normal pH. I have had good results with this powder in another case.

COKE'S CASES.

Cases 11, 58 and 88 quoted by Coke illustrate the onset of allergic symptoms following the administration of antidiphtheritic serum therapeutically. Coke attributes the effect to a disturbance of colloidal equilibrium by the serum. It seems equally likely that the associated diphtheria was responsible. B. diphtheriae is known to have an adrenalotoxic effect.

Cases 1, 21, 29, 41, 76 quoted, show freedom from allergic symptoms during War service, i.e. during exposure to cold and physical effort.

Cases 9 and 10 illustrate freedom from asthma following a pyrexia.

SUMMARY OF CASES.

Although my series of cases is comparatively small in number it illustrates several important points. Adam's week-end type is well represented. Cases 1, 2, 4 and 12 are almost certainly of this type. They all showed definite improvement with treatment designed to increase the metabolic rate by increasing exercise, increasing heat production, by diminishing clothing and by increasing sympathetic activity. This latter end is accomplished by administering a sympathetic stimulant

(ephedrine) along with a sympathetic sensitisor (thyreoid extract). It is noteworthy that in no case has an attack of asthma occurred during treatment. The associated bronchitis has been diminished, though not entirely removed in every case. In only one case, No.17, has the treatment had to be abandoned (on account of insomnia). This particular case was complicated by arteriosclerosis and chronic bronchitis.

In case 4 one attack occurred during the period included. The treatment had been interrupted for two days previously, and after six weeks of thyreoid-ephedrine therapy these drugs were stopped. One mild attack has occurred since in association with a coryzal attack. Otherwise the child is quite free from asthma with the exception of an occasional wheeze on waking in the morning.

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APPENDIX.

a. THYEROID-EPHEDRINE FEVER.

I have had two examples of fever produced by these drugs in combination. In each case the patient was in bed during treatment, and heat loss was therefore restricted.

Case 1. Eunice Westcott, aet. 4. Pertussis.
This child had had a cough for 14 days and paroxysmal coughing had begun. I did not hear her whoop, but the mother stated that she whooped on one occasion. The cough produced vomiting.
I gave thyreoid gr. 2 daily for three days, and followed by giving a mixture containing ephedrine gr. 1/16 every four hours. The child became febrile without any apparent cause. It was two days before I realised that the ephedrine was responsible. Stopping the mixture brought the temperature down inside four hours. The cough has not returned, and it seems likely that the attack was aborted by treatment. In the absence of an epidemic I have been unable to confirm this observation.

Case 2. Miss Hodges, aet. 28. Asthma.
Last attack twelve months ago. Sensible clothing, wears low neck etc.
On 31st December commenced attack, probably due to mild weather, menstruation and Christmas over feeding. I saw her on 2nd January in status asthmaticus. Adrenalin gave some relief, and an ephedrine mixture was given. Temperature following morning 99·6. She was then given thyreoid gr.5 and ephedrine gr.¼ night and morning until the morning of the 5th. Her temperature remained between 100 and 101, controlled by sponging. She had no ephedrine on the morning of the 5th, and her temperature was normal. Her attack was cured.

Pyrogenic substances (e.g. T.H.N., B. typhosus vaccine) produce sympathetic fever more readily in thyreoid fed animals and less readily after thyreoidectomy. Thyreoid-ephedrine treatment presents possibilities as a method of producing therapeutic fever, for use instead of Malaria or T.A.B. vaccine. Heat loss would require to be reduced of course. Fever is not

desired in the treatment of asthma as secondary parasympathetic effects may be produced. This is one reason for reduction of clothing (including bed clothing) in treatment.

b. SKIN TESTS.

Bray quotes a figure of less than one per cent as the frequency of positive skin reactions in normal persons, but adds that he personally has not obtained positive reactions in any healthy child or in a child suffering from a non-allergic disease. As I personally regard positive skin tests as being mainly dependent on atonicity of the skin vessels, it occurred to me to investigate the skin reactions of children recovering from diphtheria. In these children the suprarenals are presumably subnormal. Dr. Douglas of the Bradford Fever Hospital very kindly undertook to do this work for me. The only proteins used were cheese and tomato extracts prepared by Parke, Davis & Co. A control test was done in each case. 60 unselected children were tested. The results are shown in this table.

AGE GROUP	NO.	CHEESE Pos.	TOMATO Pos.	BOTH Pos.	PER CENT. Pos.
1 - 5	25	3	1	1	12%
6 - 10	16	3	1	1	18.7%
11 - 15	8	2	1	1	25%
Over 15	11	2	0	0	18.2%
All cases	60	10	3	3	16.6%

A control test was done in each case. In two cases which gave positive reactions to cheese and slight reactions to tomato when tested on the 8th and 13th days of the disease respectively, a negative response was obtained 9 weeks afterwards.

In 350 cases Coke obtained three positive reactions to cheese and six to tomatoes. These patients were suffering from asthma. If Coke's deduction from his figures is correct, and the asthma in these cases is actually due to food sensitisation, revealed by skin testing, one might expect to find that diphtheria was

also due to food sensitisation, a theory which no one would seriously uphold. Positive skin reactions merely reveal that conditions are favourable for the appearance of Lewis's wheal response, i.e. that sympathetic tone is reduced. Lewis himself mentions that the response is more likely to appear if the skin is warm.

c. MILK.

It is a curious thing that milk and milk products have a harmful action on asthmatics. Milk has been put forward as a complete food, and is much in favour even now. However, casein is known to differ from other proteins in many important respects. For instance casein has a much lower specific dynamic action than meat fibrin. As is well known, a meat diet is harmful in hyperthyroidism, while casein is definitely beneficial. The calcium content of milk may also have some influence in depressing the sympathetic system.

From a biological point of view milk is essentially a food for the young rapidly growing animal. It is not suited so well for energy production as for processes of growth and repair. The infant sleeps after his feed, and it is to his advantage to have his metabolism depressed, so long as the process is not carried too far by artificial heating. He has more material left for body-building purposes. Milk as an article of diet for an adult, however, has many disadvantages. Here energy producing food is required rather than tissue-builders, and the man who develops asthma after a glass of hot milk is paying the penalty for his unbiological habits.

Incidentally, to carry the biological theory one step further, the perfect example of parasympathetic predominance is the foetus in utero, with his total immunity from stimulation by cold, all his bodily processes devoted to growth, and his bronchioles completely occluded.