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EFFECT OF TOXIC SUBSTANCES ON THE BLOOD-FORMING ORGANS

WITH SPECIAL REFERENCE TO THERAPEUTIC DRUGS*

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The amount of a drug which will produce a therapeutic, toxic, or lethal reaction varies in different patients or animals. With certain poisons, such as digitalis, the range of variation is small; with others, such as dysentery toxin or the barbiturates, the range is wide. For a given poison the toxic symptoms are the same however much the dosage required to produce them varies in different individuals. Those who are poisoned by an unusually small dose of the substance may be said to be susceptible to it or tolerate it badly. Dudley¹ has described a striking demonstration of variation of susceptibility in a British submarine crew during the war. While the submarine was submerged there was an escape of arsine gas from the storage batteries, and the crew of thirty men, all selected for physical soundness, were exposed to exactly the same amount of arsenic for exactly the same length of time, yet they differed markedly in their response to it. One was not affected at all; seven had anaemia and jaundice (the severest case had a count of 1,980,000 red cells); the rest had symptoms of anoxaemia, but not severe enough for hospital treatment.

In susceptibility or intolerance the symptoms are the usual ones of overdosage with the particular drug. A small minority of individuals, however, react to certain drugs in a wholly abnormal manner which is properly called idiosyncrasy. Idiosyncrasy is a peculiarity of constitution whereby the individual reacts differently from the majority of mankind. The symptoms are different from the ordinary symptoms of overdosage and they cannot, as a rule, be reproduced in animals. Susceptibility shades gradually into normal tolerance and insusceptibility, and if we chart the amounts of a drug necessary to produce toxic symptoms in a large number of people we obtain a regular distribution curve similar to a diagram of variations in height or weight. Idiosyncrasy, on the other hand, is sharply demarcated. The published figures of the amounts of arsenobenzol, amidopyrine, and gold which have induced changes in the blood appear rather uniformly small, and after a certain total quantity of the drug has been administered the risk of the idiosyncratic type of reaction progressively diminishes.^{2,3} The difference between susceptibility and idiosyncrasy can be illustrated by reference to amidopyrine.

Amidopyrine Susceptibility and Idiosyncrasy

The usual symptoms of overdosage with amidopyrine are sleepiness passing to stupor, rapid heart beat, hyperpnoea, cyanosis, sweating, and collapse. The fatal dose is about 8 grams. If symptoms of this type occurred with a dose much smaller than 8 grams we should describe the patient as susceptible to amidopyrine. In certain individuals as little as 0.2 gram may produce an alarming and entirely different train of symptoms. The individual shivers and feels indisposed. The temperature rises and there is an abrupt fall in the number of white cells in the blood. Fatal agranulocytosis has more than once followed the administration of as little as 1 gram of amidopyrine over a short period of time. These symptoms are obviously different from the usual manifestations of amidopyrine poisoning and are best explained as idiosyncrasy. I wish to stress the importance of variable susceptibility and idiosyncrasy as it is still not generally appreciated. Only recently the following expert testimony was reported⁴:—

"It was not conceivable that the condition disclosed by the autopsy could have been caused by the occasional use of amidopyrine . . .

"The urine had been almost clear, whereas in a case of amidopyrine poisoning it would have been a brick red."

Both statements overlook the possibility of idiosyncrasy. Experience and statistical calculations show that the susceptibility of mankind to drugs varies within much wider limits than has been realized in the laboratory and in the law courts. Idiosyncrasy makes unreliable any calculation of dosage or prediction of symptoms from animal experiment and can only be discovered by unbiased observation of the experiment of large-scale employment in man. It appears to need at least ten years' extensive use before the harmful properties of a new drug or an industrial hazard can be assessed.

Gold Preparations

We are only now beginning to appreciate the haemotoxic properties of gold, which has been widely used for tuberculosis since Moellgaard's⁵ paper in the *British Medical Journal* in 1925, and for rheumatism since Forestier's⁶ paper in the *Lancet* in 1932. Blood dyscrasias have been observed with different preparations of gold, and they appear to be caused by the gold, and not by the sulphur

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or the benzene ring which some of the salts contain. Mercury and silver may exert a similar action on the marrow.⁷ The preparations used contain as a rule between 30 and 50 per cent. of gold. In tuberculosis it is customary to inject sanocrysin (syn. crisalbine, $\text{Au}(\text{S}_2\text{O}_3)_2\text{Na}_2$). The initial injection is 0.1 gram, increased at weekly intervals to 1 gram, and a course totalling about 6 grams is given in six or seven weeks. In rheumatism solganol-B oleosum, an oily suspension of aurothioglucose is used; injections of 0.05 to 0.2 gram are given at weekly intervals until a total of 2 grams has been given. In tuberculosis and in rheumatism courses of gold treatment are repeated several times with intermissions of two or three months. When gold treatment was first introduced, much larger doses were given, up to 1 centigram per kilo of body weight for several days in succession. The ordinary symptoms of overdosage are fever, malaise, albuminuria, stomatitis, vomiting, diarrhoea, erythema, exfoliative dermatitis, and focal reactions in the disease under treatment.

In 1932 Emile-Weil and Bousser⁸ collected thirty-two cases of haemorrhagic disease following gold treatment, and in 1935 Braillon⁹ collected twenty-six cases of agranulocytosis following gold treatment. In addition to purpura and agranulocytosis, aplastic anaemia, leukaemia,¹⁰ excessive leucocytosis,¹¹ and punctate basophilia¹² have been attributed to gold. The haemotoxic accidents of gold therapy are quite different from and are not accompanied by the ordinary symptoms of gold poisoning. It is impossible to produce a haemorrhagic state or agranulocytosis by injecting gold subcutaneously or intravenously in animals. Moreover the majority of these accidents have been after moderate doses of gold, well within the usual therapeutic limits, and during a first or second course of treatment. Various warning signs such as eosinophilia and leucopenia are described and it is obviously desirable to examine the blood at frequent intervals when gold is administered. It must be remembered, however, that eosinophilia and leucopenia occur in untreated asthma and arthritis, and a fatal blood dyscrasia may appear without any previous alteration in the blood picture. Severe haemorrhage may occur when the platelets and the bleeding time are normal and the tourniquet test is negative. It is exceedingly doubtful whether these accidents can be prevented by the simultaneous administration of calcium, as has been suggested. The accidents of gold therapy are therefore not due to carelessness or overdosage and must be attributed to idiosyncrasy. The frequency of such an idiosyncrasy is estimated by Braillon⁹ as 1 per thousand, but it may be noted that it occurred in three of Hartfall and Garland's series of 100 arthritic patients treated by gold. It is rare for a blood dyscrasia to develop within a fortnight of beginning treatment and the interval for sensitization may be much longer. The total dosage required for sensitization may be very small, as shown by the figures in the following table, which I have compiled from the published reports most easily accessible.* This shows that in 50 per cent. of the patients who develop a blood dyscrasia from gold the total dosage has been less than 2 grams, and in 75 per cent. it has been less than 4 grams of gold salt.

Total Dosage of Gold Salt	No. of Cases of Blood Dyscrasia
0.00—0.49 Grams	8
0.50—0.99 „	7
1.0 —1.99 „	10
2.0 —3.99 „	11
4.0 —7.99 „	7
8.0 — „	4

* This table is based on references 9, and 13 to 27 inclusive.

Nature of Idiosyncratic Reaction

The causes of unusual susceptibility and idiosyncrasy to a drug are obscure. Drug idiosyncrasy seems to have no aetiological relation to the toxic idiopathies or asthmac-ezema-migraine group of diseases.²⁸ A hereditary liability is suggested by the occurrence of agranulocytosis in different members of the same family.^{29, 30} Females more often develop agranulocytosis, toxic purpura, and aplastic anaemia from chemical agents than males, but they are probably more exposed to risk in health and sickness. Ohlsen³¹ passed through three attacks of agranulocytosis—two after amidopyrine and one after gold. Tzanck's³² patient developed purpura haemorrhagica after arsenobenzol treatment at age 23, and again after gold at 31. These observations suggest a constitutional predisposition, but probably once the marrow has been damaged it is more vulnerable to other poisons. Local predisposition may also be important: women who have always bruised easily have been thought to be more liable to toxic purpura from gold, and the predilection of agranulocytosis for middle-aged women may be associated with the frequent occurrence of moderate leucopenia in the same group. The disease for which the treatment is given may have an influence, and some have thought that the blood-forming organs are more likely to suffer damage from the use of gold in rheumatoid arthritis than in tuberculosis.

In some cases of idiosyncrasy, such as agranulocytosis from amidopyrine, a mechanism akin to anaphylaxis is present, an initial dose being necessary to sensitize the patient. A certain total quantity of amidopyrine, which is usually relatively small, must be ingested before this sensitization develops. The abrupt fall in the white cells when amidopyrine is ingested by the sensitized subject—sometimes preceded by a brief leucocytosis—is an explosive phenomenon which is strictly comparable to the diminution of the white blood cells in patients with food allergy.³³ Efforts have been made to obtain skin reactions by injecting the drug or mixtures of the drug with serum intradermally,³⁴ but one would hardly expect skin reactions to be any more constant or reliable than in other forms of alimentary allergy. An allergic type of reaction has also been demonstrated in thrombocytopenic purpura due to drugs, a close analogy with thrombocytopenia due to food allergy.³⁵ The allergic reaction to haemotoxic drugs is seen most clearly in amidopyrine agranulocytosis and in the purpura due to sedormid^{36, 37} and quinine,³⁸ but there is a very considerable field for experiment in discovering how often haemotoxic reactions are allergic and repeatable under controlled conditions, and in studying the exact details of the reaction by serial blood counts and examination of the bone-marrow by sternal puncture.

In a man of 61, who had taken the hypnotic sedormid (allyl-isopropyl-acetyl-carbamide) at frequent intervals for some months, an attack of thrombocytopenic purpura could be induced at will by giving 0.12 gram sedormid.³⁶ Maritschek and Markowicz's³⁹ patient was a man aged 35 who had suffered from "quinine intoxication" during treatment for malaria, fifteen years prior to coming under observation. The symptoms at that time were purpura and haemorrhages from the mucosae, and the usual manifestations of quinine intoxication were absent. There remained a persistent hypersensitivity to quinine, so that even small doses (0.3 gram) produced severe thrombocytopenia. McCarthy and Wilson⁴⁰ reported a case of thrombocytopenic purpura following arsphenamine. After recovery from the first attack the patient again received a small amount of the drug (0.1 gram). At the end of half an hour there was a slight chill with immediate development of purpura and bleeding from the gums.

Incubation and Duration

For various reasons, such as the time taken for sensitization to develop, or for toxic substances to accumulate to a critical level in the body, or for repeated injuries to exhaust the reserve forces of the organism, signs of injury to the blood-forming organs may not be detected until the individual has been exposed to a toxic substance for some time or indeed until after exposure has ceased. It seems that injury to the marrow, once started, may progress without further intoxication. Alice Hamilton⁴¹ quotes several instances in which symptoms of benzol anaemia did not appear until after the workers had left the factory. In one of Hartfall and Garland's cases¹³ agranulocytosis developed three months after the last injection of gold. In one of my cases agranulocytosis developed two months after the last dose of amidopyrine. It is not known how long amidopyrine sensitivity lasts, but certainly for years, and possibly for life. As already indicated, the depression of blood formation induced by a substance like benzol may proceed inexorably to complete aplasia of the marrow and to death long after exposure has ceased, and despite all treatment. If death does not occur, months may elapse before the blood is restored to normal, and cases such as those of Ohlsen¹¹ and Tzanck²² make one wonder whether recovery is ever really complete. In patients with agranulocytosis it is usually six to twelve months after suspension of amidopyrine before the white count is stabilized at a normal level, and doubtless much longer before the ability to produce a maximal leucocytosis is regained. The toxic purpuras usually recover more rapidly, but Secher²² describes a case in which thrombocytopenia following gold treatment had persisted for six months at the time of writing. A severe aplastic anaemia is usually fatal, but a few cases have recovered after repeated transfusion over a period of years. The case of hyperchromic anaemia in a benzol-worker reported by Emile-Weil and Lehmann recovered rapidly on liver therapy only.⁴² The case of aplastic anaemia due to benzol reported by Hayhurst and Neiswander recovered after six transfusions given over a short period.⁴³ Knott's case of aplastic anaemia from arsenobenzol resulted in death from pneumonia after receiving fifty-two blood transfusions in a period of eighteen months.⁴⁴

Classification

In the past attention has been too exclusively centred on the changes in the circulating blood, and insufficient attention has been paid to the marrow. This gap in our knowledge should be filled now that we are becoming more accustomed to puncture or trephine the sternum during life. The same blood picture may be associated with quite different appearances in the blood-forming organs, and in particular we are beginning to realize that an aplastic blood picture may be associated with a marrow which is hyperplastic but fails to deliver new cells into the circulation. It is a mistake to regard the blood disorders produced by chemical substances as different from other blood disorders. There are striking resemblances between the changes in arsenobenzol purpura and infective endocarditis; between the bone-marrow in malaria and in radium poisoning. Classification of the lesions must be regarded as arbitrary, for they shade indefinitely into one another or are combined in varying degrees. The same drug may produce different lesions in different people or at different periods after exposure in the same person.

Out of seventy-seven blood counts in benzol poisoning there were seventeen with a blood picture such as one sees in benzolized animals—that is, a leucopenia far in excess of the

anaemia; but there were twenty-two with the reverse—excessive anaemia with moderate leucopenia or a normal white count. Typically the red cells should present a perfectly negative picture, but this is not always true. We may find abnormalities of size, shape, staining properties; we may find stippling, and even nucleated red cells. A review of seventy-five cases shows that while the colour index was low in seventeen, in twenty-two it was high, and in thirty-six it was normal. Haemorrhage is usually a conspicuous feature, but it is not invariable. The marrow is not always aplastic; it may show hyperplasia, but with a failure to deliver the new cells into the circulation.⁴¹

It is convenient to divide blood poisons into those which act on the peripheral blood and those which act on the marrow. The division is not hard and fast, and many substances act in both situations. In benzol or gold purpura, haemorrhage may occur without any change in the platelets or bleeding time, suggesting that the endothelium is involved. When amidopyrine is taken by the sensitized individual the white blood count falls spectacularly, suggesting that the drug acts on the circulating cells as well as on the leucopoietic tissue. I do not propose to discuss in detail the haemolytic and haemotoxic poisons which act on the circulating blood and produce according to their nature anaemia, methaemoglobinaemia, or polycythaemia. Arsine, toluylenediamine, and lead are the most important of the haemolytic agents, the aniline compounds the most important of the haemotoxic, but the ingenuity of the chemist is constantly adding new members to the series. The reactions of the marrow can be briefly tabulated as follows:—

1. Regenerative hyperplasia, as after haemorrhage or arsine poisoning.
2. Dysplasia, in which the marrow is cellular, but the ripening of the cells is imperfect and few are delivered into the circulation.
3. Neoplasia—that is, leukaemia.
4. Aplasia.

Dysplasia

Any over-elaboration of this classification would be merely an academic exercise, more especially as reliable data on the morbid anatomy of the marrow are scanty and the lesion is often a mixed one. In the majority of cases in which marrow activity is inhibited but not destroyed, the number and proportion of the different cells is the same as in health, but various degrees of degeneration may be found in the cells according to the severity of the lesion, the freshness of the material, the refinement of the staining, and the self-confidence of the pathologist. These are the same changes as are familiar to us in other organs under the title of parenchymatous degeneration, and they may affect more severely the megakaryocytes or the myelocytes with consequent purpura or leucopenia. In this category I should place the usual acute effects of benzol and its derivatives, arsenobenzol, dinitrophenol, nirvanol, thorium dioxide, and gold. If the patient survives the acute attack, the marrow more or less rapidly recovers, but this is not always the case, for sometimes a lasting torpor or paralysis may ensue, in which few blood cells are produced by the marrow, although it appears relatively normal to the naked eye and to the microscope.

It has only recently been realized how often a progressive anaemia of aplastic type proves at necropsy to be associated with a marrow of normal or increased cellularity.⁴⁵ I prefer to describe this type of dysplasia of the marrow as pseudo-aplastic anaemia. The erythropoietic tissue is more resistant than the leucopoietic tissue or the megakaryocytes, and when the formation of red cells is inhibited there is usually depression of white cells and platelets also. Israëls and Wilkinson⁴⁶ have designated

"achrestic anaemia" (formerly "achrestic") certain cases of anaemia with megalocytosis and hyperplastic marrow which do not respond to liver, implying that they are caused by inability to utilize or mobilize the material needed by the pernicious anaemia patient. I have already mentioned that a megalocytic anaemia and hyperplastic marrow may occur in benzol poisoning, and I do not like the term "achrestic anaemia" if it implies that these conditions have a real affinity to Addison's anaemia. The few examinations of the marrow we have made in patients who answer the criteria of "achrestic anaemia" have shown a cellular marrow with many large erythroblasts, but in spite of a considerable megalocytosis there were none of the primitive megakaryoblasts (haemocytoblasts) which are so typical of pernicious anaemia. It is probable that any of the poisons which produce aplasia of the marrow can also arrest the maturation of the cells without actual necrosis and aplasia, and produce a pseudo-aplastic anaemia.

In the usual form of dysplasia, red cells, white cells, and platelets are involved together, though in varying degree, and the cytology of the marrow does not differ greatly from the normal. This is not always the case. The agranulocytosis produced by amidopyrine is a lesion strictly limited to the white cells and the leucopoietic tissue; the erythropoietic tissue and the megakaryocytes are normal, but the development of the white cells is arrested at the myeloblast level, and few myelocytes and polymorphonuclear cells are produced. The state of affairs is similar to the megaloblastic degeneration of the marrow in Addison's anaemia. Such a maturation arrest or anaknesis, as it has been called,⁴⁷ in which the marrow contains a normal or increased number of primitive or stem cells but maturation is inhibited, may affect the leucopoietic, megakaryocytic and erythropoietic tissues, either separately or together. In essential thrombocytopenia there is an increased number of megakaryocytes and megakaryoblasts in the marrow, although the number of platelets in the circulating blood is diminished,⁴⁸ and one may well suspect a similar state of affairs in sedormid purpura. In the anaemia of radium poisoning, more particularly the form due to the ingestion of radio-active material and internal irradiation of the marrow,⁴⁹ the marrow is extremely hyperplastic, as a result chiefly of arrest in development of the erythropoietic tissue and accumulation of immature erythroblasts. In most instances the dysplastic marrow of poisoning must be the result of a mixture in varying degree of degeneration, anaknesis, and aplasia. The variation in the degree of involvement of red corpuscles, leucocytes, and platelets in different toxicoses and the variety of the bone-marrow changes have given rise to great confusion in terminology. This applies particularly to the term agranulocytosis, which should be reserved for a lesion limited to the polymorphonuclear cells of the blood and characterized by arrest of maturation in the leucopoietic tissue. Constant additions to terminology are to be deprecated, and more use should be made of accurate descriptive names such as leucopenic leukaemia, arsphenamine purpura, benzol leucopenia, pure agranulocytosis, etc.

Neoplasia

The dysplastic bone-marrow is in an unstable condition. We have evidence that in agranulocytosis the maturation arrest of the leucocytes ultimately ends in aplasia of the leucopoietic tissue of the marrow. The long duration of some cases of aplastic anaemia is hard to reconcile with the complete disappearance of marrow cells seen at necropsy and suggests an intermediate phase of unproductive hyperplasia. This suspicion is strength-

ened by the fact that cases of benzol poisoning which present an identical blood picture in life may prove to have either a cellular or an aplastic marrow. A more difficult question is whether arrest of the normal development of the cells does not sometimes lead to the uncontrolled proliferation of leukaemia. The difficulty is that leukaemia is not an uncommon disease, and coincidence must therefore be excluded.

Rolleston concludes that the induction of leukaemia by α rays and radium has not been proved.⁵⁰ On the other hand Levent states that leukaemia is five times as common in physicians practising radiology as in their colleagues.⁵¹ In experimental animals leukaemia has been induced by indole,⁵² benzol,⁵³ and tar,⁵⁴ and there is therefore good reason for considering leukaemia in benzol workers^{51 55} as more than a coincidence. In a remarkable case reported by Falconer, a patient under treatment for chronic benzol poisoning with an aplastic type of anaemia gradually developed the picture of lymphatic leukaemia.⁵⁶

Aplasia

If the blood-forming organs are overwhelmed by a poison the stem cells die and the marrow becomes aplastic. Among substances capable of producing this degree of damage we may enumerate benzol and some of its derivatives such as arsenobenzol, dinitrophenol, and trinitrotoluene; mercury, silver, and gold; radium, and α rays. An injury so severe is unlikely to be confined to a single haemopoietic element, and usually red cells, white cells, and platelets are involved simultaneously. I have already mentioned, however, that in the late stages of agranulocytosis there may be a pure destruction of the leucopoietic tissue or granulo-phthisis. In other cases the destruction of the megakaryocytes is disproportionate (thrombophthisis or purpura maligna), though the severity of this condition depends as much on the torpor of the leucopoietic and erythropoietic tissues as on the intensity of the haemorrhagic state. As will be understood from what has already been said about the greater resistance of the red cells, the white cells and platelets are usually more severely affected, but this hardly justifies the introduction of the term aleukia haemorrhagica for cases in which white cells and platelets are predominantly involved. In conclusion I should like to stress my belief that the section of pathology with which I have been dealing is top-heavy with terminology and under-ballasted with facts. We need more histological data on the marrow not only from necropsies, but also from serial observations during life. We also need more clinical experiments, in which the effects of drugs to which patients appear sensitive are tested under controlled conditions. The interest of the subject should not be limited to haematologists, as it promises to throw light on the general problem of idiosyncrasy.

Summary

1. The toxic effects on the blood-forming organs of drugs such as amidopyrine, neoarsphenamine, and gold are usually the result of idiosyncrasy and occur with doses that are well within the ordinary therapeutic limits.
2. In certain cases the patient becomes sensitized to the drug and an allergic type of response occurs.
3. Considerable hardship may result from failure to realize the small dosage which may be responsible for damage to the bone-marrow in predisposed individuals, the long incubation period, and the protracted duration of the lesion.
4. The lesions produced in the marrow are briefly reviewed and classified under the headings of regenerative hyperplasia, dysplasia, neoplasia, and aplasia.

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J. C. Hughes, O. A. Dietheim, and A. H. Tebbutt (*Med. Journ. of Australia*, March 7th, p. 327), who report a fatal case of typhus in a man aged 44, state that the twenty-nine cases of typhus reported or notified in New South Wales during the last nine years were restricted to two widely separated areas—namely, the metropolitan area of Sydney and the far north-eastern area bordering on Queensland. In both these districts the disease appears to be on the increase. A similar distribution occurs in the south and west of Australia. A. H. Tebbutt and D. A. Warden (*ibid.*, p. 330) report another case of typhus, the patient being a woman aged 55 living in a good house in a first-class residential district in Sydney. The symptoms were fever of fourteen days' duration, lethargy or drowsiness, slight prostration, but no splenic enlargement; the Weil-Felix reaction was positive on the eleventh day. Recovery took place.

PHYSICAL METHODS OF ENDOCRINO-THERAPY*

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One of the most important recent advances in the science of disease is the recognition and study of the metabolic endocrine disturbances which precede local organic conditions. It has been shown that the external morbid factors act first of all on the system integrating the body, a system constituted by the psycho-associational cortex, the vegetative nervous system, and the endocrines. Reactions on disturbances of this system precede and dominate local organic manifestations. Treatment of these disturbances, by helping this integrating system to re-establish its normal function, is the basis of modern internal medicine. The endocrines play an important part in this mechanism of biological integration. There are conditions in which the endocrine organs show predominant manifestations in what we rather artificially describe as "endocrine diseases." In all morbid conditions, however, we have to take into consideration the endocrine-metabolic disturbances, and their treatment is of the greatest importance.

Treating Endocrine Disturbances

Therapeutic action on the endocrine organs can be effected by various methods, first by endocrine organotherapy, using the glandular products themselves. In substitution organotherapy the glandular secretions in which the patient is deficient are given; this is the most potent procedure, although the indications for it are limited. Less effective is stimulating organotherapy, in which an endeavour is made to stimulate a deficient endocrine by giving glandular products. An endocrine can never be stimulated by its own product; an indirect route is therefore necessary, and the product of another endocrine which works on a superior level must be used, as when we stimulate ovarian function by the administration of pituitary.

Organotherapy, however, is not the whole of endocrinotherapy. We can affect the endocrines by other methods—by psychotherapy, by dietetics, and by certain drugs—but principally by physical methods. Biology gives us the basis of physical endocrinotherapy. The endocrines function according to external stimuli, the stimuli of physical environment. Physical medicine consists in a scientific study and utilization of these stimuli of our physical environment. The action of physical agents on endocrine function is effected through four distinct mechanisms, acting often in combination:

1. The ionic equilibrium mechanism.
2. The skin endocrinotropic mechanism.
3. The nervous reflex mechanism.
4. The direct glandular mechanism.

Ionic Equilibrium Mechanism

The ionic equilibrium mechanism re-establishes a normal ionic equilibrium through physical agents. As normal ionic equilibrium means normal permeability of the cellular membrane and normal reactivity of the cells, re-establishment of this equilibrium renders the cells more susceptible to hormonal influences. In many so-called endocrine disturbances there is a normal production of hormones, but, as the cells are not permeable to them, endocrine

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