system, might seem to favour the virus hypothesis. On the other hand, the failure so far to transmit the experimental disease in animals, and the absence of immunity after recovery do not support the view that the active principle is of virus nature. Finally, there is the possibility that the substance may be of the nature of an enzyme, producing specific damage to the central nervous system.

The problem is one of the greatest interest and practical importance, and the data given in this paper are put forward as a further contribution towards its study. Whether or not the encephalitogenic agent is directly related to Hodgkin's disease, the fact remains that it is of clinical importance in the diagnosis of the condition, and as a new pathogenic principle merits the most careful investigation.

CONCLUSIONS

1. Twenty cases of Hodgkin's disease and thirteen other conditions of lymphadeno-hypertrophy have been investigated. Gordon's biological test gave positive results in fifteen (75 per cent.) cases of Hodgkin's disease, and was found to be negative in the others.

2. The occurrence of a reaction in the rabbit closely simulating Gordon's encephalitic syndrome has been observed to follow intracerebral inoculation with bone marrow derived from a case of acute myelogenous leukaemia.

3. The encephalitogenic agent in Hodgkin's disease has been found to exhibit the following properties: (*a*) The maximum quantity is liberated from Hodgkin lymphatic tissue when buffered phosphate broth of *p*H 7.1 is used for its emulsification. (*b*) Alkalis, such as sodium hydroxide, sodium bicarbonate, ammonia, and ammonium carbonate, may all cause considerable reduction in the pathogenicity of active material. (*c*) Tissue emulsions have been frozen to −190° C. for ten minutes and tissue desiccates for twelve hours, without inactivation. (*d*) The agent resists exposure to ten unit skin doses of *x* rays. (*e*) It can be readily adsorbed in neutral solutions by kieselguhr, less so by carbon particles, and least of all by normal rabbit brain. (*f*) It can be passed through Berkefeld (British) and Sietz (EK) filters.

The writer desires to thank the clinicians and pathologists at the Royal Infirmaries of Edinburgh and of Glasgow, and at other institutions in Scotland and England, who so willingly co-operated in the investigations. He is greatly indebted to Drs. J. Duncan White and C. M. Scott for their assistance in connexion with the *x*-ray experiments, and to Professors Mackie and Drennan for their valuable advice and helpful criticism.

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A new edition of the *Official Guide Book of Medical Post-Graduate Work in Hungary* has just been issued by the Hungarian Medical Post-Graduate Committee (VIII, Mária-utca 39, Budapest). This excellently illustrated volume contains full details in English of the various hospitals and clinics where all kinds of medical post-graduate work can be undertaken. It is stated that all the professors and chief physicians speak English, French, or German. In addition to its main office in Budapest, the Post-Graduate Committee has subcommittees in the other university towns, and arrangements for study can be made wherever desired. Much modernization of the existing institutions has been effected in the last few years, and several new medical buildings have been erected. The *Guide Book* contains also information about places of historic interest in Hungary. There are now in that country four medical faculties, with 4,520 beds available for medical and post-graduate training, as well as 21,534 beds in the large public hospitals.

THE USE OF 2:4-DINITROPHENOL AS A METABOLIC STIMULANT

BY

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It has been known since 1885[1] that nitrated naphthols can stimulate metabolism, and during the war attention was called to their toxic effects owing to the incidence of poisoning among workers in munition factories. A review of these effects was made by Perkins,[2] and they were more recently commented on by the Council of Pharmacy and Chemistry of the American Medical Association.[3] Only incomplete investigations of the pharmacological action of such compounds were, however, made till 1928, when Heymans[4] and his co-workers revived interest in the subject by a series of publications which showed that certain nitrophenols are powerful stimulators of metabolism, causing a greatly increased oxygen consumption. When a considerable dose is taken the endogenous heat production may be so stimulated as to cause a rise of temperature, and death from a lethal dose occurs during a hyperpyrexia. The lethal dose of dinitrophenol for rats has been shown by Anderson, Reed, and Emerson[5] to lie between 30 and 50 mg. per kilo of body weight, but doses as small as 5 mg. per kilo of body weight may produce pyrexia in man, and it has been stated that the margin between the febrile and fatal dose is narrow.

During the last two years Magne, Mayer, and Plantefol,[6] and Cutting and Tainter,[7] have published reports on the main pharmacological actions of dinitrophenol. All these workers are agreed that the action of the drug in stimulating the metabolic rate is peripheral, due to an increased oxygen consumption in the tissues, and is independent of nervous and glandular action. In considering the source of the fuel for the increased metabolism they are also agreed that the body proteins are not broken down to any appreciable extent. The French workers, however, observing in the experimental animal under the influence of dinitrophenol a marked decrease of the carbohydrate content of the body, particularly in respect of the liver glycogen, and a corresponding rise in the blood sugar, argued that the excess metabolism was mostly at the expense of carbohydrate. The experimental and clinical studies of Cutting and Tainter, on the other hand, failed to reveal any difference between the excess metabolism due to dinitrophenol and that occurring normally. The latter workers, using this drug in doses of 3 to 5 mg. per kilo of body weight, have recommended its use in the treatment of obesity, and have recently published encouraging results from extended clinical trials in which an average daily oral dose of 0.3 gram (5 grains) of the drug was administered to 113 consecutive cases of obesity without drastic dietetic restrictions. No severe cumulative or toxic effects were produced, though most of the patients noticed a sense of increased warmth and increased sweating, while in 7 per cent. of them a skin rash occurred, and in 5.3 per cent. there was a loss of taste. These side actions cleared up quickly, without sequelae, on discontinuing the medication. Anderson, Reed, and Emerson[5] have also treated fourteen cases of obesity, using similar doses of the drug, and obtained some slight loss in weight without much dietetic restriction. In one patient, however, they obtained a serious allergic skin and joint reaction. This patient suffered from chronic articular rheumatism, and it is suggested that individuals suffering from this complaint have a lessened resistance to the agent. Indeed, Perkins,[2] in his review of the poisonous effects of dinitrophenol on

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munition workers, reported that cases of chronic rheumatism, alcoholic addiction, diabetes mellitus, tuberculosis, and renal and hepatic insufficiency were particularly sensitive to it.

In addition to dinitrophenol, a related compound, dinitro-*o*-cresol, has been reported on by Dodds and his co-workers.[8] They claim it to be considerably more active than dinitrophenol, and stress, as other workers have done in the case of dinitrophenol, that neither the pulse rate nor the blood pressure is raised in any way proportionately to the height of the metabolism. Dodds further states that toxic symptoms are occasioned by dinitro-*o*-cresol when the metabolic rate is raised by its means to over 50 per cent. above the patient's normal. He mentions particularly sweating, lethargy, headache, loss of appetite, and a greenish-yellow tinge in the conjunctivae. This latter symptom has also been noted by Tainter, using dinitrophenol, but neither worker discovered any excess bile pigments to be present in the blood of such cases; and it must also be remembered that the drugs themselves are dyes producing much the same colour as bile pigments.

The fact that drugs of this type have specific powerful effects in raising metabolism, without at the same time causing tachycardia, combined with their cheapness and availability, might strongly recommend them as superior to other metabolic stimulants in general therapeutic use. On the other hand, Dodds[8] has suggested that in spite of their effects on metabolism such drugs do not act as a substitute for thyroid in hypothyroid states, except in so far as they may reduce excess body weight. Further, it has yet to be demonstrated that they are as safe and efficient for weight reduction in human beings as other methods in common use. It may indeed be argued that so many toxic reactions have been produced in the relatively small number of cases treated that the use of such compounds is not as yet clinically justifiable on a large scale, and that their popularization as weight reducers might well be disastrous. It is therefore of importance that careful pharmacological investigations and cautious clinical trials of these new and powerful products should be made before their widespread application is undertaken.

METHOD

The effects of 2:4-dinitrophenol on human beings, when administered orally in gelatin capsules, were studied over a considerable period of time under carefully controlled conditions in hospital. The subjects were three obese women. In Cases 1 and 2 the patients had normally mildly reduced basal metabolic rates, while Case 3 presented the typical features of advanced myxoedema. The drug was given to Case 1 in single doses of 2 mg. per kilo of body weight, several days being allowed to elapse between each dose. Metabolic readings were made before the drug was given, and at intervals of a quarter of an hour afterwards for two hours, and thereafter every morning until the metabolism had for some days returned to its normal base line. This procedure was repeated on four occasions. Case 2, after a considerable control period, was given dinitrophenol in doses rising from 1 to 3 mg. per kilo of body weight, the metabolism being allowed to reach a constant maximum for each quantity of the drug before the dose was increased. The effects were contrasted with those produced by a daily dose of 6 grains of thyroid. Case 3, after a similar control period, was given a daily dose of 3 mg. per kilo of body weight, and the effects again contrasted with those produced by 6 grains of thyroid daily, and also with those occasioned by 50 mg. of di-iodothyronine daily, a synthetic preparation reported on by Anderson, Harington, and Lyon.[9]

Throughout their stay in hospital the patients had their diets kept constant in respect of total calories and in respect of the content of fat, carbohydrate, and protein. With the object of giving the patients a diet just sufficient to maintain their weight while leading a sedentary life, without supplying material for luxus consumption, the diets for the three individuals varied between 1,800 and 2,000 calories. Fluids were not limited. The patients were weighed daily at the same hour. The basal metabolism and respiratory quotients were determined daily, early each morning, using the Douglas bag and Haldane gas analysis apparatus, and all the determinations were made in duplicate. Twenty-four-hour specimens of urine were collected and measured daily, and were then examined for abnormal constituents, their total nitrogen content being estimated by the micro-Kjeldahl method. The pulse and blood pressure were noted daily under basal conditions, and the blood urea, sugar, cholesterol, and icteric index were frequently determined. A four-hour oral temperature chart was kept, and in Case 2, on three occasions, a continuous temperature chart, galvanometrically recorded by means of an electric thermo-couple strapped into the axilla, was kept for two hours before, and for twenty-two hours after, the administration of dinitrophenol.

BASAL METABOLIC RATE

In each case dinitrophenol was found to have a powerful effect in raising metabolism and in increasing oxygen consumption. The absorption of the drug was exceedingly rapid, a noticeable effect being produced on the metabolism a quarter of an hour after the oral administration of a single dose, and a maximum effect for the day being produced in an hour's time. This effect would last almost unimpaired for twenty-four hours, but in forty-eight hours the metabolism had invariably fallen to a level only slightly above its original value.

TABLE I.—*Effect on Four Occasions of 2 mg. per Kilo of Body Weight of Dinitrophenol on the Metabolism of Case 1*

	I	II	III	IV
Basal	− 16	− 9	− 14	− 16
¼ hour after dinitrophenol	− 3	+ 7	± 0	− 3
¾ hour " " ...	+ 2	+ 11	+ 10	+ 2
1 hour " " ...	+ 7	+ 21	+ 16	+ 7
1¾ hours " " ...	+ 4	+ 21	+ 14	+ 4
24 hours " " ...	+ 7	+ 8	+ 8	+ 7
48 hours " " ...	—	− 8	+ 1	—
72 hours " " ...	− 9	− 12	− 5	− 9

With the daily administration of the drug the metabolism rose rapidly on the first day, and on subsequent days continued to rise slightly. A maximum level was reached about the fourth day, at which point it remained, fluctuating within very narrow limits, till an increased dose sent it up still further, or the withdrawal of the drug brought it rapidly to normal. For all practical purposes the effect on the metabolism, even after prolonged administration, had worn off within seventy-two hours of the withdrawal of the drug. The rapidity with which the action of the drug on the metabolism wears off, and the rapidity with which its effects become manifest, are thus in marked contrast to the slow onset and slow subsidence of thyroid action, the effects of which only become apparent some three to four days after its administration is started, and continue for five to six days after it has been withdrawn.

The action produced by dinitrophenol was found to be fairly proportional to the dosage employed. In Case 1, where single doses of 2 mg. per kilo of body weight were given, the metabolism twenty-four hours later was invariably found to be increased by almost exactly 23 per cent. In Case 2, where different doses were employed, 1 mg. per kilo of body weight produced an average maximum rise in metabolism of 12 per cent., 2 mg. of 25 per cent., and 3 mg. of 35 per cent. In Case 3, where 3 mg. per kilo of body weight were given, an average maximum rise of 42 per cent. was produced.

URINARY NITROGEN AND RESPIRATORY QUOTIENT

Dinitrophenol exerted no significant influence on the excretion of urinary nitrogen. This contrasts with the very considerable increase in nitrogen excretion observed

TABLE II.—*Effect of Dinitrophenol and Thyroid on the Excretion of Urinary Nitrogen*

Average Urinary Nitrogen Excretion in Grams per Day.

	Case 1	Case 2	Case 3
Control period	9.44	8.56	7.80
Dinitrophenol period ...	9.00	9.09	8.61
Thyroid period	—	12.15	11.91

in patients undergoing treatment with thyroid, in which respect the cases under consideration were no exception. It is apparent, therefore, that the excess metabolism due to dinitrophenol is not conducted at the expense of exogenous or endogenous protein to any appreciable extent, whereas a small but significant part of the excess metabolism produced by thyroid *is* due to protein.

Reference to Chart II shows that a considerable fall in the respiratory quotient occurred during the period of dinitrophenol administration to Case 3, the average basal respiratory quotient for the control period being 0.84, while on dinitrophenol the average was 0.74. Again, in Case 1, where frequent determinations were made during the two hours following the administration of single doses of dinitrophenol, a tendency for the respiratory quotient to fall was usually noted, and there was never a significant rise. In Case 2 the respiratory quotient remained remarkably low throughout the control period, and remained low during the whole period of dinitrophenol administration (see Chart I). In the present series of experiments the exhibition of thyroid caused no very significant variation in the respiratory quotient, though our previous experience suggests that on the average the effect of thyroid is to raise the respiratory quotient slightly.[10]

These results would seem to indicate that the excess metabolism produced by dinitrophenol is conducted at the expense of fat rather than at the expense of carbohydrate or protein, though this interpretation is subject to the criticism that the method of approach is an indirect one. From the fact that no ketone bodies were ever discovered in the urine, it would seem that any fat used was completely and satisfactorily broken down.

PULSE AND BLOOD PRESSURE

No important increase in pulse rate or change in blood pressure was produced by dinitrophenol, a 40 to 50 per cent. increase in metabolism being associated with a pulse rate raised by less than ten beats per minute. These observations are in remarkable contrast to the well-known effects of thyroid on the circulation, which so often contraindicate its use in cases of obesity. In Case 3, for example, a metabolic increase of only 20 per cent. induced by thyroid resulted in the pulse rate being accelerated by twenty-four beats a minute, and caused the patient to complain of palpitation. This constitutes a distinct advantage of dinitrophenol over thyroid extract or thyroxine, but in one respect it is a drawback, since no conception of the extent of the metabolic increase can be gauged from the state of the pulse ; and the only methods of evaluating the metabolism under dinitrophenol are by resort to the somewhat cumbrous procedure of determining the basal metabolic rate, or by relying on the subjective sensations of the patient, which may on occasion give an erroneous impression. Di-iodothyronine, which in all other respects appears to produce the same metabolic and endocrine effects as thyroid, seems to have a less severely disturbing influence on the circulation.

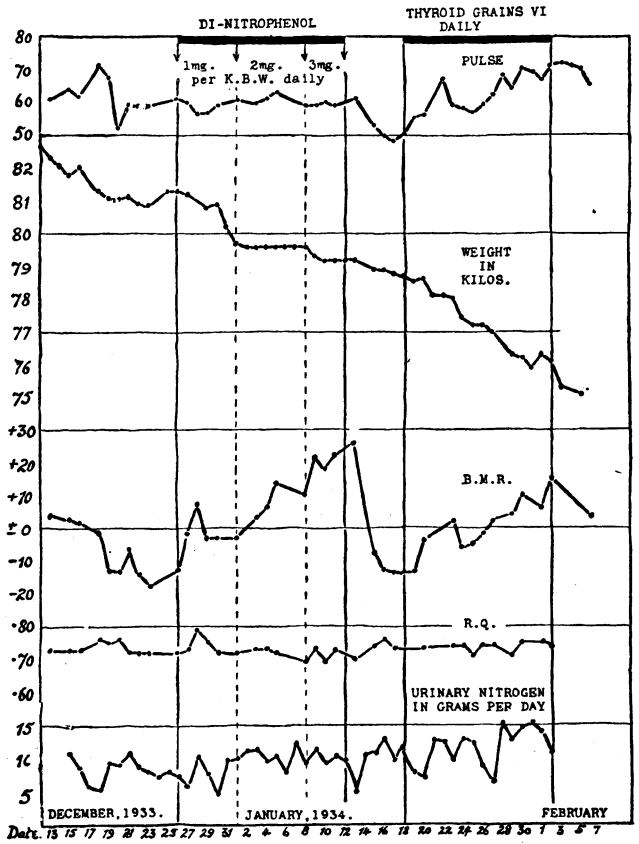

CHART I.—Effect of dinitrophenol and thyroid on Case 2.

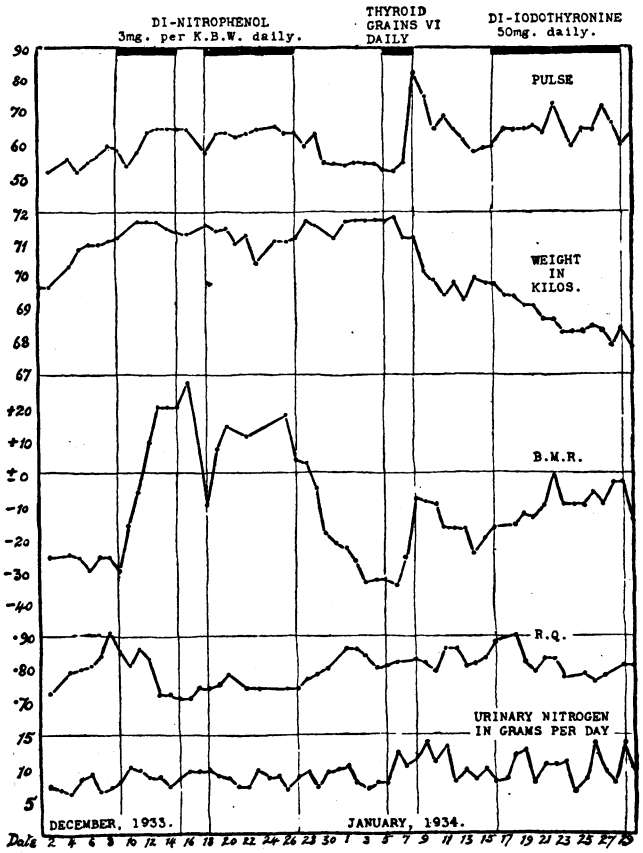

CHART II.—Effect of dinitrophenol, thyroid, and di-iodothyronine on Case 3.

WEIGHT

TABLE III.—*Average Effect of Dinitrophenol and Thyroid on Weight in Kilos per Week*

	Case 2	Case 3
Control period	Loss of 0.70	Gain of 1 33
Dinitrophenol period ...	Loss of 0.84	No change
Thyroid period	Loss of 1.47	Loss of 2.10
Di-iodothyronine period ...	—	Loss of 0.77

It will be seen that the weight loss produced by dinitrophenol was exceedingly disappointing, and that the great increase in metabolism which it occasioned was associated with a loss of weight quite insignificant in comparison with that produced by thyroid, in spite of the fact that the metabolism was not raised to anything like the same extent by the latter. This disparity in results can only be explained by the fact that thyroid exercises a marked effect on the partition of water in the body, whereas dinitrophenol is ineffective in this respect, in spite of the considerable sweating which it induces. Indeed, the actual loss of weight under dinitrophenol approximated closely to the loss calculated from the metabolic results on the basis that no change in water balance occurred. A comparison of the percentage of average urinary output to intake during the control, dinitrophenol, and thyroid periods gives suggestive results.

TABLE IV.—*Effect of Dinitrophenol and Thyroid on the Average Percentage of Urinary Output to Fluid Intake*

	Control Period	Dinitrophenol Period	Thyroid Period
Case 2	66 per cent.	62 per cent.	83 per cent.
Case 3	87 „	74 „	102 „

In a previous comparison of the therapeutic effects of diet and thyroid in the treatment of obesity we have shown that approximately 9 grains of thyroid daily are required to cause a fall in weight equivalent to that produced by treatment with a diet of 1,000 calories[11]—a dosage seldom tolerated by the obese patient. Since thyroid is itself, apparently, a very much more efficient weight-reducer than dinitrophenol, it would appear that exceedingly toxic or even lethal doses of the latter would be required to ensure the same effect as that produced by diets of 1,000 calories.

OTHER EFFECTS

As long as the metabolic increase effected by dinitrophenol was not more than 30 per cent. above the patient's normal the subjective sensations experienced were not unpleasant. Indeed, with small increases in metabolism a rather pleasurable sensation of comfortable warmth was produced. With a greater elevation, however, uncomfortable symptoms of heat and sweating were experienced, and with a rise of over 40 per cent. the patients were considerably distressed by these effects, and complained of lethargy and exhaustion. Notwithstanding this, no significant elevation of the temperature was noted on any occasion, even when this was continually recorded over a period of twenty-four hours by a sensitive electric thermo-couple strapped into the axilla. Apparently it was therefore possible, with the doses used, for the endogenous heat production to be satisfactorily dissipated.

Apart from the symptoms mentioned, no toxic effects were occasioned by dinitrophenol, and the palpitation, invariably experienced by the patient in Case 3 when given thyroid, was noticeably absent while she was receiving this drug. An insignificant increase in the blood sugar occurred under dinitrophenol, while there was a similar insignificant increase in the blood urea under thyroid medication. The blood cholesterol and icteric index were unaffected, and no abnormal contents were produced in the urine.

In spite of its effects on metabolism dinitrophenol is apparently no substitute for thyroid. Case 2 was just as myxoedematous, with a basal metabolism of +18, the result of nearly three weeks' treatment with dinitrophenol, as she was previously with a basal metabolism of −30. On the other hand, small doses of thyroid, thyroxine, or di-iodothyronine, sufficient to raise the patient's metabolism to a figure no higher than − 10, speedily improved her myxoedematous symptoms and appearance.

CONCLUSIONS

Dinitrophenol is a powerful and rapidly acting stimulant to oxidative metabolism, which does not at the same time upset the pulse rate or the blood pressure. The excess metabolism, which subsides rapidly when the drug is withdrawn, is conducted largely at the expense of fat. In doses of 3 mg. per kilo of body weight it may increase the metabolism to as much as 50 per cent. over its original level, though the average increase is usually less than this amount. No serious toxic effects were produced by such a dose in the present investigation, though such are recorded in the literature. Uncomfortable sensations of excessive warmth, sweating, and lethargy may, however, be complained of, which may necessitate the average dose being less than 3 mg. per kilo of body weight. In such doses dinitrophenol is likely to be singularly ineffective in lowering excess body weight, and even in maximum therapeutic doses it does not compare, as a weight reducer, with thyroid, and still less with dietetic restriction. It is no substitute for thyroid in myxoedematous states.

I am indebted to Professor D. M. Lyon for the opportunity of carrying out this investigation.

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The Import Duties (Drawback) (No. 2) Order, 1934, issued by the Treasury on March 8th on the recommendation of the Import Duties Advisory Committee, provides, under Section 9 of the Finance Act, 1932, for the allowance of drawback of customs duties for a period of twelve months in respect of castor seed used in the manufacture of exported castor oil. Following the imposition in March, 1932, of the general *ad valorem* duty on castor seed there has been a great reduction in the imports of foreign seed into the United Kingdom, and it is represented that the removal of the British buyer from the market has materially contributed to the fall of the world price of foreign seed to a level which gives the foreign seed crushers an advantage over British crushers in the export markets for castor oil. The granting of drawback will substantially restore to the British crushers economic freedom in the choice of seed required for their export trade in castor oil, which in 1933 amounted to nearly £250,000. A White Paper containing the Treasury Order and the Advisory Committee's recommendation is published by H.M. Stationery Office (Cmd. 4532).