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Hypertensive Interactions Between Monoamine Oxidase Inhibitors and Foodstuffs*

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Introduction

Hypertensive attacks during treatment with amine oxidase inhibitors were first described in tuberculous patients, and were "rediscovered" when these drugs were introduced into psychiatry. In an assessment of iproniazid for tuberculosis (Ogilvie, 1955), 4 out of 42 patients experienced "attacks of a most distressing nature", with severe throbbing occipital headache and high blood pressure. Six years later, similar attacks were observed in 5 out of 212 patients treated for depression with nialamide (Davies, 1959), but it was not until the introduction of tranylcypromine that reports again appeared (Lurie and Salzer, 1961; Clark, 1961). By the beginning of 1963, over 40 such cases had been reported, including several complicated by intracerebral haemorrhage or cardiac failure due to the rise in blood pressure (Songco, 1961; McClure, 1962; Dorrell, 1963).

In a few instances amphetamine produced identical symptoms of headache and hypertension in patients taking an amine oxidase inhibitor (Zeck, 1961), but most cases were considered idiosyncratic drug responses (Womack, 1963a). The fact that patients continued taking the amine oxidase inhibitor without further adverse effects (Burke and Lees, 1963) might have suggested an unidentified precipitant. Davies (1959) considered that alcohol fulfilled this role, and Lurie and Salzer (1961) noted attacks in two patients "after the ingestion of a heavy meal". Following a report of a hypertensive crisis (Blackwell, 1963a), Rowe (personal communication, 1963) suggested cheese as a provocative agent. The text of his letter is given below:

"You might be interested in a few details concerning two severe attacks, similar to those you describe, which my wife recently experienced during treatment with 'Parstelin' tablets. As a pharmacist I have taken particular interest in the treatment.

"*Episode 1:* After cheese on toast; within a few minutes face flushed, felt very ill; head and heart pounded most violently, and perspiration was running down her neck. She vomited several times, and her condition looked so severe that I dashed over the road to consult her G.P. He diagnosed 'palpitations' and agreed to call if the symptoms had not subsided in an hour. In fact, the severity diminished, and after about three hours she was normal other than a severe headache—but 'not of the throbbing kind'. She described the early part of the attack 'as though her head must burst'.

"*Episode 2:* One week later, again after eating cheese on toast. This episode was even more dramatic; the vomiting and throbbing headache lasted beyond the early hours of the morning and even at 10 a.m. the next day she was very ill. Symptoms subsided in about 24 hours.

"Could there be a link between the effects and the amino acids of the cheese? No effects are caused by butter or milk. Although treatment with Parstelin has continued no further episodes have occurred. If cheese is indeed the factor, it could perhaps explain the sporadic nature of incidence of the side-effect. I hope my comments will be of some use to you in your investigations."

Enquiry into the diet of our first patient revealed that she had probably eaten cheese before the attack. Soon afterwards two other in-patients taking monoamine oxidase inhibitors suffered from headache and hypertension one hour after eating cheese. Between January 1963 and June 1964, 20 cases of hypertensive crisis were referred by consultant psychiatrists at the Bethlem Royal and Maudsley Hospitals and 5 by general practitioners.

Findings in the first 12 cases referred were described at the start of the investigation (Blackwell, 1963c). A further 13 cases are now

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presented, and findings in the total of 25 patients are compared with those in a control group of 50 out-patients prescribed monoamine oxidase inhibitors at the Maudsley Hospital during January and February 1965. In addition, tests with foodstuffs were made in selected patients. The object of these investigations has been to define the characteristics of the reaction and the factors in patients or treatment which influence susceptibility. Our findings are discussed in relation to pharmacological tests in animals (Blackwell and Marley, 1964, 1966a and b; Blackwell, Marley and Mabbitt, 1965) and to chromatographic analyses of foodstuffs (Blackwell and Mabbitt, 1965).

Results

A. *Reactions to Foodstuffs*

Clinical features: Data from the 25 patients are summarized in Table I. The reactions, which varied greatly in severity and duration, were unrelated to physical activity, posture or emotion, but occurred within 10-135 min. of the ingestion of certain foodstuffs. During the reaction, the patient experienced a forceful increase in heart beat ("palpitations") accompanied by throbbing of the blood vessels in the neck and followed within minutes by a severe pulsating headache of sudden onset. This was at first confined to the occipital or temporal regions, but later became generalized. During the attack the patient sometimes felt flushed or perspired profusely (9 subjects). Seven patients complained of neck stiffness or photophobia, even though subarachnoid haemorrhage did not occur. Vomiting or nausea occurred in 8 patients, and the picture was then one of extreme prostration. The onset of symptoms was sudden, and of the 13 patients whose blood pressure was recorded (Table I) the mean increase in systolic pressure (55 mm. Hg) exceeded that of the diastolic (30 mm. Hg). The threshold at which severe throbbing headache commenced varied, but the systolic pressure was usually in the region of 200 mm. Hg or over, and the headache remitted as the blood pressure fell to normal. The duration of the attacks varied from 10 minutes to 6 hours during which the hypertension and headache fluctuated in severity. Changes in pulse rate and rhythm were occasionally observed. Of ten patients seen during the reactions, bradycardia accompanied the rise in blood pressure in five cases and coupled beats or irregularities in rhythm were noted in two (cases 10 and 11).

Recovery was complete except for intracerebral bleeding proven by lumbar puncture in four patients (cases, 5, 7, 9 and 23) with a fatal outcome in one (No. 9) and a left hemiplegia lasting six weeks in another (No. 7). A third of the patients experienced further mild headaches for several days following an attack, but unprovoked by food. In two patients (cases 4 and 24) there was a subsequent period of hypotension with systolic blood pressure below 90 mm. Hg, lasting 12 and 36 hours respectively.

B. *Incidence*

Twenty-three new out-patients began taking monoamine oxidase inhibitors in each month of the control period. The monthly total of tablets prescribed to them was 10,500, compared with 12,000 during the time when the 20 cases were referred. Correcting for this 12·5 per cent. decline in the use of monoamine oxidase inhibitors from 1963 to 1965, the estimated number of new patients treated in each month of the referral period was 26. On this basis, 468 patients were at risk during the 18 months in which 20 cases of hypertensive crisis were reported, an incidence of 4·3 per cent. of all patients taking monoamine oxidase inhibitors between January 1963 and June 1964.

C. *Dietary Precipitants*

A dietary history was taken, except in two cases where this was impossible because of the death of the patient (case 9) or lapse of time (case 7). Of the remaining 23 patients, 17 had eaten cooked or raw cheese before an attack, two had taken a yeast extract, 'Marmite', and one had eaten cheese and Marmite together. Three patients had not eaten these substances, but the antecedent foods were pickled herring, tinned milk, and a dehydrated high-protein product, 'Complan'.

Fourteen patients were in the habit of eating

TABLE I

Some Clinical Features in 25 Cases of Hypertensive Crises

Case No.	Sex	Age	Drug	Dosage (mg.)	Duration of treatment	Dietary peculiarities	Antecedent food factor	Delay to onset	Blood pressure (mm.Hg*)	Duration of headache	Complications
1	F	34	Tranylcypromine	10 b.d.	8 weeks	Vegetarian	Cooked cheese	1 hr.	220/115 (110/70)	2 hr.	
2	M	36	Tranylcypromine	10 t.i.d.	5 days	Obesity	Raw cheese	2 hr.	Not known	3 hr.	
3	F	16	Tranylcypromine	10 b.d.	8 weeks	Mixed	Raw cheese	45 min.	220/130 (140/70)	1 hr.	
4	F	24	Tranylcypromine	10 b.d.	9 weeks	Anorexic-'Complan' Low carbohydrate	Raw cheese	40 min.	180/100 (110/70)	1½ hr.	
5	F	49	Tranylcypromine	10 b.d.	9 days	High protein	'Marmite'	2 hr.	ot known	5 days	Subarachnoid haemorrhage
6	F	32	Tranylcypromine	10 b.d.	3 weeks	Obesity	Cooked cheese	1 hr.	Not known	15 min.	
7	F	43	Tranylcypromine	10 b.d.	16 months	Mixed	Not known	1½ hr.	170/100 (160/90)	10 min.	Hemiplegia for 6 weeks
8	M	39	Tranylcypromine	10 b.d.	6 days	Mixed	Raw cheese	1 hr.	Not known	1½ hr.	
9	F	49	Tranylcypromine	10 t.i.d.	15 days	Not known	Not known	Not known	160/100	Not known	Died with intracranial haemorrhage
10	F	43	Phenelzine	15 t.i.d.	5 weeks	Mixed	Raw cheese	1 hr.	200/100 (130/70)	30 min.	Coupled beats
11	F	50	Tranylcypromine	10 b.d.	4 weeks	Mixed	Raw cheese	2½ hr.	200/100 (120/70)	1⅔ hr.	Irregular cardiac rhythm
12	F	43	Tranylcypromine	10 b.d.	3 days	Anorexic-'Complan'	'Complan'	2 hr.	Not known	1 hr.	
13	F	42	Phenelzine	30 t.i.d.	4 years	Mixed	Raw cheese	1 hr.	Not known	3 hrs.	
14	M	37	Mebanazine	5 t.i.d.	4 weeks	Obesity	Raw cheese	30 min.	150/100 (130/85)	1 hr.	
15	F	51	Pargyline	50 mane	6 weeks	Mixed	Cheese & 'Marmite'	20 min.	Not known	30 min.	
16	F	43	Phenelzine	30 b.d.	6 months	Obesity (1,000 calories)	Raw cheese	30 min.	170/100 (150/85)	5 hr.	
17	F	32	Tranylcypromine	10 t.i.d.	5 weeks	Anorexic	Tinned milk	1 hr.	200/110 (140/90)	6 hr.	
18	F	33	Phenelzine	15 t.i.d.	7 weeks	Mixed	Raw cheese	2 hr.	Not known	20 min.	
19	M	37	Tranylcypromine	20 b.d.	4 weeks	Obesity	Raw cheese	1 hr.	Not known	2 hr.	
20	F	23	Tranylcypromine	10 b.d.	2 days	Mixed	Raw cheese	2 hr.	Not known	1½ hr.	
21	M	42	Tranylcypromine	10 t.i.d.	2 weeks	Mixed	Pickled herring	10 min.	180/120 (120/80)	3 hr.	
22	F	40	Phenelzine	30 t.i.d.	12 weeks	Mixed	Cooked cheese	45 min.	Not known	30 min.	
23	F	58	Tranylcypromine	10 b.d.	18 months	Mixed	Raw cheese	30 min.	Not known	1½ hr.	Subarachnoid haemorrhage
24	F	29	Phenelzine	30 t.i.d.	4 weeks	Mixed	Raw cheese	45 min.	186/120 (125/70)	15 min.	
25	F	39	Tranylcypromine	20 b.d.	18 months	Anorexic	'Marmite'	20 min.	200/105 (125/80)	45 min.	

* Normal values in parentheses

cheese at least once a week and 4 ate it daily. Over half the patients had therefore eaten cheese at some previous time in treatment without experiencing adverse effects. In the control series of 50 patients on monoamine oxidase inhibitors, 12 had eaten cheese and 6 had taken Marmite in the preceding month without ill-effect. The fact that many patients taking monoamine oxidase inhibitors suffered no consequences from eating cheese or Marmite suggested that there might be undetected variables in the characteristics of the individual patient or the type of treatment they were receiving.

D. *Individual Characteristics*

The control group and the 20 Bethlem and Maudsley patients were compared to determine if there were any features which might dispose an individual to hypertensive attacks.

(*i*) *Age and sex*

Drug metabolism differs between the sexes and sometimes varies with age (Kalow, 1965). In this study these variables did not contribute to liability to hypertensive attacks. Thus, the mean age of patients experiencing reactions was 37·6 years (range 16-58 years) and of the control group taking monoamine oxidase inhibitors, but without reactions, was 39·7 years (range 19-60 years). Both groups were predominantly female (75 per cent. and 70 per cent. respectively), as expected in psychiatric outpatients with depressive illness.

(*ii*) *Personality factors*

Because neurotic patients sometimes show an exaggerated blood pressure response to physical or psychic stress (Malmo and Shagass, 1952), Dally (1965) suggested that only patients with reactive (neurotic) depression suffer hypertensive side-effects from the use of monoamine oxidase inhibitors. This impression may have originated from the fact that monoamine oxidase inhibitors are not often prescribed to the older patient with "endogenous" depression. This was endorsed by the finding of a mean age below 40 years in both patient and control groups. We doubt if this factor is important, since neurotic features were mentioned in the notes of 65 per cent. of patients and 54 per cent. of controls. Hypertensive crises occurred in two patients (case 11, and test 2 reported below) with "endogenous" depression, and stable premorbid personality.

(*iii*) *Liability to headaches*

Bram (1963) suggested that patients taking monoamine oxidase inhibitors who experienced headaches following ingestion of food precipitants were those with "a predisposition to cerebrovascular insufficiency" and a previous history of headaches. This suggestion is not supported by the finding that 48 per cent. of the controls, but only 30 per cent. of patients, tended to suffer from severe headaches. The features of the headache reported in this study were typical of those noted in people who experience a sudden major elevation in blood pressure (Wolff, 1963), and it was characteristic that patients who suffered a hypertensive crisis described the pain as unlike any previous headache they had experienced.

(*iv*) *Tissue stores of catecholamines*

The hypertensive crisis has been likened to the rise in blood pressure due to sudden secretion of catecholamines from adrenal medullary tumours, but the excretion of vanillyl mandelic acid (VMA), was normal in the urine collected from three patients in the 24 hours following a hypertensive crisis (cases 3, 4 and 11).

(*v*) *Drug metabolism*

The rate of metabolism of isoniazid by acetylation of the amino group is determined by a dominant autosomal gene (Evans, Manley and McKusick, 1960). Tuberculous patients who inactivate isoniazid slowly have higher tissue concentrations of the non-metabolized drug and experience more side-effects than patients who are rapid inactivators (Devadatta *et al.*, 1960). Phenelzine and tranylcypromine are likely substrates of the enzyme responsible for metabolizing isoniazid, and Evans, Davison and Pratt (1965) found that the severe side-effects (not including hypertensive crises) experienced by 47 depressed patients taking phenelzine occurred among slow inactivators of isoniazid.

The possibility that patients who had suffered hypertensive attacks due to food were also slow inactivators of isoniazid was examined. Venous

blood was taken from seven patients 6 hours after an oral dose of isoniazid (60 mg./kg. 'metabolically active mass' or weight to the power of 0·7). The plasma isoniazid level was then determined by the method of Maher *et al.* (1957) and results are given in Table II.

Four patients were rapid and three slow inactivators of the drug. Further study was not undertaken, since these figures accord with the gene distribution in the normal population, and both slow and rapid inactivators suffered from hypertensive attacks.

TABLE II

Isoniazid inactivator type in patients who experienced a hypertensive crisis

Case No.	Inhibitor	Isoniazid Inactivator type
1	Tranylcypromine	Rapid
3	Tranylcypromine	Slow
19	Tranylcypromine	Slow
20	Tranylcypromine	Slow
22	Phenelzine	Rapid
24	Phenelzine	Rapid
25	Tranylcypromine	Rapid

E. *Variables in Treatment*

Apart from individual differences between patients, the sporadic incidence of hypertensive crises and apparent dietary immunity of some of the subjects could have been due to differences in their treatment.

(*i*) *Type of amine oxidase inhibitor*

To assess the relation of drug structure to the incidence of side-effects depends upon the extent to which the different compounds are prescribed. The use of the different inhibitors was compared in the control series and in the 20 Bethlem and Maudsley patients (Table III).

TABLE III

Use of different monoamine oxidase inhibitors in patients suffering hypertensive crises and a control group

Drug	Patient (N=20)	Control (N=50)
Phenelzine	20%	48%
Tranylcypromine	75%	36%
Others	5%	16%

Phenelzine and tranylcypromine (including 'Parstelin') accounted for 90–99 per cent. of all the monoamine oxidase inhibitors prescribed to hospital patients during the period of investigation. Small numbers of patients were prescribed isocarboxiazad, nialamide, or iproniazid. Throughout the trial, the number of cases with hypertensive crises due to tranylcypromine was higher than expected if use alone was responsible. The final assessment was that 75 per cent. of cases (15 patients) were due to tranylcypromine, which accounted for only 40 per cent. of use, whereas 20 per cent. of cases (4 patients) were due to phenelzine, which was prescribed in 55 per cent. The degree of risk associated with tranylcypromine and phenelzine can be calculated by applying these data on usage to the estimated number of patients at risk. 40 per cent. of the 468 patients were taking tranylcypromine, so that 15 cases of hypertensive crises occurred in 186 patients. 55 per cent. of patients were treated with phenelzine, and 4 cases occurred in 257 patients at risk. The relative incidence of hypertensive crisis was 8 per cent. of patients treated with tranylcypromine and 1·5 per cent. of those given phenelzine. The risk associated with tranylcypromine was therefore five times greater than with phenelzine.

(*ii*) *Dosage and duration of treatment*

Hypertensive crises occurred in patients treated with normal dosage of monoamine oxidase inhibitors for periods varying from two days (case 20) to 18 months (cases 23 and 25). However, there were differences in the duration of treatment for the cases due to tranylcypromine and those caused by phenelzine. There were also differences in dose between the patient and the control group in which there was a similar range of treatment duration.

The mean daily dose in patients was 25 mg. of tranylcypromine (15 patients) and 79 mg. of phenelzine (4 patients), but the mean daily dose of the compounds in the controls was 30 mg. and 45 mg. respectively. The duration of treatment with tranylcypromine was often shorter than with phenelzine. Thus 6 patients (40 per cent.) had taken tranylcypromine for 15 days or less before the incident but none had received

phenelzine for under four weeks. This suggested that tranylcypromine was more likely to cause a hypertensive crisis than phenelzine when both were given in therapeutic doses.

F. *Tests in Patients*

Previous observations in man (Blackwell, 1963c) and in animals (Blackwell and Marley, 1964, 1966a) left no doubt that cheese could provoke hypertension, but confirmation that Marmite was also responsible and further investigation of the variable factors in treatment necessitated tests in patients. They were conducted on two patients under carefully controlled conditions, after the risks had been explained and the tyramine content of the Marmite had been assayed in pithed rats.

Patient 1: This patient (No. 25 in Table I) who had been taking tranylcypromine for 18 months had experienced many typical attacks provoked by cheese or by the yeast extract Marmite (Blackwell, Marley and Ryle, 1964). She was admitted for investigation, and a series of tests were made using graduated amounts of Marmite dissolved in warm water. The patient was starved overnight and given her usual morning dose of tranylcypromine (20 mg. by mouth). Two hours later she was given Marmite to drink. Blood pressure and pulse rate were recorded every 5 minutes by the same observer and with the patient recumbent. The results are given in Table IV, and recordings from two tests (4 and 6) are shown in Fig. 1 (A, B).

Rises in blood pressure only occurred when sufficient Marmite was given (3 g. or over), but the magnitude of the response varied with the same dose (compare tests 2 with 3, and 4 with 5). The rise in blood pressure began

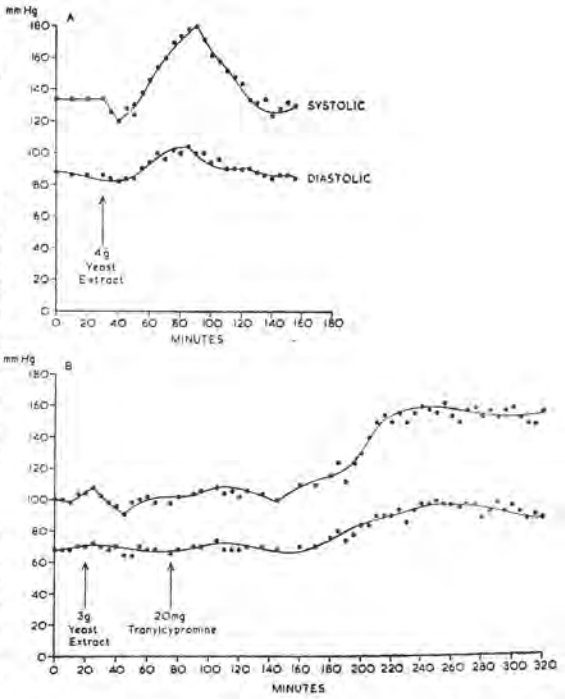

FIG. 1.—Effects of yeast extract 'Marmite' on systolic and diastolic blood pressure of a patient treated with tranylcypromine (Case 25).

A:—Yeast extract (4 g.) orally *2 hours* after tranylcypromine (20 mg. orally). Blood pressure rise begins 30 minutes after yeast extract.

B:—Yeast extract (3 g.) orally *18 hours* after tranylcypromine (20 mg.) orally. Followed by tranylcypromine (20 mg.) orally during experiment. No rise in blood pressure until 90 minutes after tranylcypromine.

TABLE IV

Effects of yeast extract ('Marmite') on blood pressure in man (a) *2 hours after tranylcypromine (20 mg. orally)*

Test	Yeast Extract (g. orally)	Rise in B.P. (mm./Hg) Systolic	Diastolic	Time (min.) after Yeast Extract Onset	Peak	Duration
1	1·5	—	—	—	—	—
2	3	50	20	15	70	150
3	3	40	15	15	40	90
4	4	50	20	20	60	100
5	4	75	25	20	65	165

(b) *18 hours after tranylcypromine (20 mg. orally) and followed by tranylcypromine (20 mg. orally) 1 hour after yeast extract*

6	3	55	30	55	140	+200
7	4	25	20	65	140	+180

15-20 minutes after taking Marmite, reached a peak after 45-75 minutes, and returned gradually to normal within one to three hours. In two of the tests (3 and 5) the electrocardiogram was recorded and an increase in the size of the T waves paralleled the rise in blood pressure. In test 5 a few extra-systoles occurred when the blood pressure was rising rapidly.

A severe throbbing headache was experienced by the patient only in test 5, and remitted when the blood pressure fell. In this test the patient also complained of feeling flushed and sweated profusely, but in all other tests she remained free of symptoms.

In two further tests (Nos. 6 and 7, Table IV), the morning dose of tranylcypromine was omitted so that the Marmite was given 18 hours after the last tablet. In both cases the yeast extract failed to raise the blood pressure. An hour later a further dose of tranylcypromine (20 mg. orally) was given and after about an hour the blood pressure rose gradually and remained elevated for over three hours (Fig. 1B). In two control experiments the blood pressure was unchanged by tranylcypromine alone (20 mg. orally).

Patient 2: Tests were made on a patient (not listed in Table I) treated with phenelzine 15 mg. t.d.s. for several weeks. During this time she had eaten large quantities of Marmite on frequent occasions with no ill effects. Tests were designed to study this apparent immunity and to investigate the part played by dosage and duration of treatment.

Phenelzine was first discontinued for five days. The patient was then given 30 mg. phenelzine orally t.d.s. (twice the daily dose on which she had been immune from hypertensive effects with yeast extract). After the first dose of phenelzine, the Marmite (10 g. dissolved in 250 ml. water) was taken by mouth 90 min. later. The Marmite was derived from the same source in all tests. (Assay of this Marmite on the blood pressure of a pithed rat showed it to contain a pressor substance equivalent in activity to 2·3 mg. tyramine per g. of yeast extract).

Administration of Marmite after the first dose of phenelzine was ineffective on blood pressure (not shown in Table V). After six days' treatment, the same amount given under identical conditions produced a small rise in blood pressure (Test A: Fig. 2. Table V). On the following day (test B) the dose of phenelzine before the test was increased to 45 mg. and the blood pressure response was doubled in size and prolonged (compare A with B, Fig. 2). After further treatment, tests were repeated on the 13th and 14th day and much larger rises of blood pressure occurred (compare in Fig. 2, A with D, preceding dose of phenelzine 30 mg.; and B with C, preceding dose of phenelzine, 45 mg.). On the 15th day when the dose of phenelzine was omitted (test E), hardly any change in blood pressure occurred.

The only symptom noted in these tests was an increased forcefulness of heart beat during the two largest rises in blood pressure (C and D). In 4 of 6 tests, the rise in blood pressure was preceded by a slight fall.

These tests confirmed that the pressor effects of the yeast extract were influenced both by the duration of treatment with the monoamine oxidase inhibitor and by the size and proximity of the preceding dose.

Discussion

1. *The Historical Perspective*

In 1846, Liebig isolated a new amino-acid from cheese and named it "tyrosine" after the Greek word meaning cheese. By the early years of this century the amine derivative, tyramine, had been extracted from cheese (Van Slyke and Hart, 1903) and its pharmacological properties were investigated by Dale and Dixon (1909). They found that tyramine caused hypertension in man and animals, and one of the experimenters recorded a rise in his own blood pressure together with "a feeling of fullness in the head" after taking the amine by mouth. In 1911, Findlay showed that 20-80 mg. of tyramine elicited rises of blood pressure within 10 minutes of intramuscular injection; the largest increases were accompanied by "excruciating headaches". He concluded, "in the cerebral arteries there was also a considerable rise in pressure—

Table V

Blood pressure response to standard doses (10 g. orally) of yeast extract ('Marmite') after various doses of phenelzine

Test	Antecedent dose of Phenelzine (mg.)	Duration of treatment (days)	Rise in B.P.		Time (min.) after Yeast Extract		
			Systolic	Diastolic	Onset	Peak	Duration
A	30	6	22	18	12	25	50
B	45	7	40	16	10	40	65
C	45	13	70	20	15	40	90
D	30	14	65	24	25	35	70
E	0	15	20	—	20	30	40

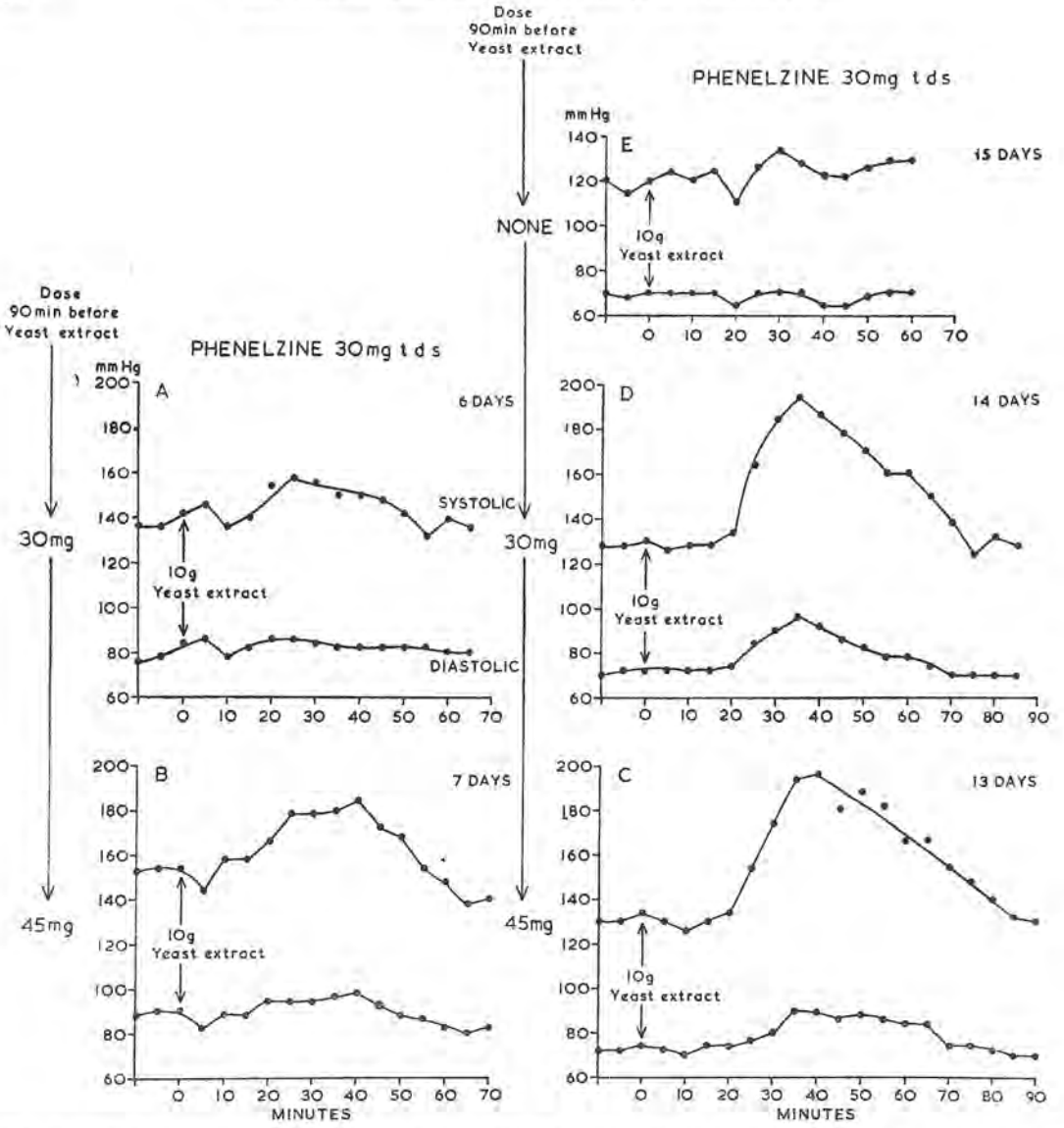

FIG. 2.—Effects on blood pressure of yeast extract 'Marmite' (10 g. orally) in a patient treated with phenelzine (30 mg. t.d.s.) showing effect of duration of treatment and size of antecedent dose of inhibitor. For details see text.

a point which would make me very careful of its use, as to my mind the risk of cerebral haemorrhage must be considered".

By this time, Metchnikoff (1903) had focused attention on the possible absorption of "ptomaines" from the gut, and the ensuing controversy culminated at meetings of the Royal Society of Medicine (Proc. Roy. Soc. Med., 1913). The symptoms attributed to intestinal toxaemia included headaches and fluctuations in blood pressure, and among the foodstuffs singled out were cheese, yeast and herring (Dixon, 1913; Saundy, 1913).

Much of the evidence was later justly

described as "unscientific or pseudoscientific" (Alvarez, 1924). Somerville (1913) pointed out that amines in foodstuffs were unlikely to reach the circulation and cause symptoms unless oxidizing machinery in the gut wall was impaired. This observation anticipated the discovery 15 years later of the enzyme responsible for oxidative deamination which was called "tyramine oxidase" after its first substrate (Hare, 1928), but was later renamed monoamine oxidase. The enzyme is present in high concentrations in the gut and liver of most species, including man. Its purpose there has been regarded as someting of an "enigma" (Davison, 1958), but in 1952 Blaschko speculated that it might serve as a "detoxicating agent, particularly if the food has been exposed to putrefaction and amines are already in it when eaten".

2. *The Clinical Syndrome and its Incidence*

During one of the earliest trials of a monoamine oxidase inhibitor, iproniazid, in the treatment of tuberculosis, Ogilvie (1955) observed headache and hypertension in patients taking it. Davies (1959) gave an excellent description of the same condition in psychiatric patients. Although official information (*Medical Letter*, 1962, and *Prescriber's Journal*, 1962) contained no warning of the risks of hypertension and headache with monoamine oxidase inhibitors, the three carefully observed cases by Clark (1961) in hospital practice and the six cases described by Brown and Waldron (1962) in general practice should have provoked concern.

Failure to recognize the syndrome was contributed to by a number of factors. Six of our cases presented as subarachnoid haemorrhage, and four patients were admitted to neurosurgical wards. Villiers (1966) reported thirteen such patients seen in neurosurgical practice during 18 months where the cause of haemorrhage was only detected after admission. In milder cases, diagnosis was hampered by the short-lived and self-limiting nature of an attack. The doctor, usually the general practitioner, was frequently unaware of treatment prescribed by others. Psychiatric patients often experience bodily manifestations of anxiety, including headache, and the blood pressure would seldom be measured in a patient with this complaint. The fatal case in this series (No. 9) was initially diagnosed as hysteria. Half the patients in the control group normally experienced severe headaches, and only two of the 50 were free of this symptom.

Since this study began and the syndrome was first described (Blackwell, 1963c) its clinical features have been confirmed (Mann and Laing, 1963; Cooper *et al.*, 1964; Bethune, Burrell, Culpan and Ogg, 1964), although doubt about the incidence of the condition has persisted. This is illustrated by a range of incidences from under 1 per cent. up to 20 per cent. of patients treated with tranylcypromine in different series from 1961 to 1964 (Table VI). The extreme figures of 0·28 per cent. and 20 per cent. were published at the same time in the *Lancet* (Cooper *et al.*, 1964) and in the *British Medical Journal* (leading article, 1964) but both were based on retrospective data, and the lower figure was derived by the manufacturers from a questionnaire circulated to psychiatrists. The incidence of 8 per cent. in this series for tranylcypromine is close to the mean incidence of 9·9 per cent. for all series reported. The overall incidence for patients taking monoamine oxidase inhibitors is probably lower. It was 4·3

TABLE VI

Reported incidence of hypertensive crises due to tranylcypromine

Author	Year	Incidence %
Lurie and Salzer	1961	2·4
Clark	1961	10
Brown and Waldron ..	1962	4
Burke and Lees	1963	18
Gates	1963	15
Richmond and Roberts ..	1963	18
Mann and Laing	1963	9
Bethune *et al.*	1964	8·4
Cooper *et al.*	1964	20
Blomley	1964	3·4
British Medical Journal ..	1964	0·28
Mean incidence (all series)	9·9%	
This series	1963–1964	8%

per cent. in this series, but would clearly depend upon the type of drug used. Twenty-six cases of intracranial haemorrhage and 9 deaths (Table VII) have been recorded, but information available to the F.D.A. in America suggested that there had been 38 cases of intracerebral bleeding and 21 deaths (Sadusk, 1964). Since recognition of the syndrome and the institution of warnings about diet, the frequency of the hypertensive crisis elsewhere (Bethune *et al.*, 1964) and in this hospital has dwindled.

TABLE VII

Incidence of intracranial haemorrhage and fatalities in patients taking monoamine oxidase inhibitors

Inhibitor	Intracranial haemorrhage No. cases	Deaths
Tranylcypromine	23	9*
Phenelzine	3	—

* Includes 3 deaths due to cheese, 3 due to amphetamine, and 3 due to unknown precipitant

3. *Dietary Precipitants and their Constituents*

(*a*) *Cheese:* Cheese was the first dietary precipitant identified (Blackwell, 1963b), causing 80 per cent. of the cases of hypertension provoked by food (Table VIII). Foster (1963) reported 25 patients treated with monoamine oxidase inhibitors in whom cheese provoked severe headache, and Davies (1963) recorded 14 incidents. Before cheese was suspected,

TABLE VIII

Food precipitants of reactions in patients treated with monoamine oxidase inhibitors. Data from world literature (references in Blackwell, 1966)

	No. Cases
Cheese	67
Alcohol	5
Yeast Products ..	3
Cream*	3
Broad beans	2
Pickled herring ..	2
Chocolate	1

* Includes 1 patient in this series not previously reported

Womack (1963a) reported the death of a young man taking tranylcypromine and attributed it to idiosyncrasy, but later concluded that cheese had provoked the fatal hypertensive episode (Womack, 1963b). Further clinical observations strengthened the evidence concerning cheese (Blackwell, 1963c; Cooper *et al.*, 1964), and tests in man and animals confirmed the association (Blackwell and Marley, 1964; Natoff, 1964; Horwitz *et al.*, 1964; Blackwell and Marley, 1966a). The suggestion by Asatoor, Levi and Milne (1963) that tyramine was the main pressor component of cheese was also confirmed.

(*b*) *Yeast extracts:* The original series of twelve patients (Blackwell, 1963c) included one who had eaten the yeast extract Marmite before an attack of headache and hypertension. Since then two further patients have been seen (case 25 and Patient 2). Harper (1964) reported a case caused by the yeast and meat extract 'Bovril' which contains added Marmite. The association between Marmite and hypertension was confirmed by investigations in two patients. Biological and chemical tests have shown that yeast extracts contain tyramine and histamine (Blackwell, Marley and Mabbitt, 1965; Blackwell and Marley, 1966b); the hypertensive effects of yeast extracts can be attributed to the presence of tyramine, although histamine may contribute to the headache. The absorption of histamine from the gut is facilitated in cats by amine oxidase inhibitors (Blackwell and Marley, 1966b). Although in the present study allergic complaints were not exacerbated during treatment with a monoamine oxidase inhibitor (Blackwell, Marley and Taylor, 1965), deterioration in nearly half of asthmatics receiving different inhibitors was reported by Mathov (1964).

(*c*) *Broad beans:* There are two accounts of attacks precipitated by eating broad beans (Hodge, Nye and Emerson, 1964; Blomley, 1964). Hodge *et al.*, showed in the rat that the hypertension was due to the amino acid "dopa" present in bean skins being converted to dopamine. Experiments in rats suggested that part of the rise in blood pressure was due to an action of the amino acid (Blackwell and Marley, 1966a).

(*d*) *Alcohol:* Alcohol may precipitate hypertensive attacks (Davies, 1959; Bethune *et al.*, 1964). Horwitz, *et al.* (1964) estimated the tyramine in several alcoholic beverages and found that wine may contain up to 25 μg/ml. of tyramine, probably sufficient to provoke hypertension in patients taking an amine oxidase inhibitor.

(*e*) *Other foods:* Nuessle, Norman and Mille (1965) reported a hypertensive crisis provoked by pickled herring, and found that the fish meat contained 3·03 mg./g. tyramine. A similar case occurred in this series (No. 21).

Chocolate, which contains a catechol derivative, vanillin, formed during the fermentation of cocoa beans, has also been incriminated (Krikler and Lewis, 1965). Milk, cream (Bethune *et al.*, 1964) or Complan, which have a high amino-acid content, may possibly provoke hypertension if amines are formed from them by intestinal decarboxylating bacteria. Tests in rats and cats pre-treated with amine oxidase inhibitors and given chocolate, cream or processed cream by intraduodenal injection, have not elicited untoward reactions (Blackwell and Marley, unpublished). However, tyrosine (Martin, 1942) added to the diet of young rats caused a variety of phenomena, including systolic hypertension. Martin concluded, "the blood pressure of normal animals may be affected by diets containing an amino-acid composition which would yield on decarboxylation predominantly pressor amines". These results were later attributed to the use of immature animals with low concentrations of intestinal monoamine oxidase (Epps, 1945).

4. *Causes of Variation in Response to Food Substances*

Initially there was a natural reluctance to accept as causal the unlikely association between eating cheese and experiencing headache and hypertension. A major reason for scepticism was the observation that many patients taking an M.A.O. inhibitor ate cheese with impunity, and over half the patients in this study had been similarly exposed to risk without ill effect during treatment before they suffered a hypertensive crisis. It would have been wrong to infer on these grounds that no causal connection existed; it suggested that other variables must influence the outcome. Immunity or susceptibility could have been due to factors in the patient, in his treatment, or in the composition of the food.

A. *Individual Variables*

Comparisons between the patients and control group suggested it was unlikely that age, sex, personality or liability to headaches would increase susceptibility to hypertensive attacks provoked by food. Rate of drug metabolism, determined by isoniazid clearance, did not appear to be related to liability to attacks, although this conclusion depends on the assumption that phenelzine and tranylcypromine are metabolized like isoniazid by N-acetylation. It was interesting to note that large rises in blood pressure were unaccompanied by discomfort in the two patients investigated. The threshold at which severe headache occurred differed between patients. In some, a rise of 60 mm. Hg systolic pressure produced severe head pain, whilst in one patient tested a 70 mm. Hg rise on two occasions caused no concern. Hodge *et al.* (1964) recorded a case in which a 120 mm. Hg rise in systolic pressure was asymptomatic. This variation in symptom threshold would clearly reduce the number of cases of hypertension brought to medical notice. The number of patients taking monoamine oxidase inhibitors who experience small but asymptomatic rises in blood pressure is probably far larger than generally supposed.

B. *Variables in Treatment*

Several factors in treatment influence susceptibility to hypertensive effects of food.

(*a*) *Type of monoamine oxidase inhibitor:* Tranylcypromine was the inhibitor mainly associated with hypertensive crises (Table IX). The extent of use could not by itself account for the preponderance of patients experiencing hypertensive attacks who had been taking this drug. Marks (1965) calculated that tranylcypromine caused 82 per cent. of all reactions, although the drug accounted for only 43 per cent. of the total prescribing of monoamine oxidase inhibitors in this country. Phenelzine was used nearly as much (36 per cent.), but caused only 8 per cent.

TABLE IX

Monoamine oxidase inibitors incriminated in reactions. Data from world literature (references in Blackwell, 1966)

	No. Cases
Tranylcypromine* ..	195
Phenelzine*	30
Nialamide	9
Iproniazid	7
Pargyline	4
Isocarboxazid ..	2
Mebanazine ..	1

* Includes cases in this series not previously reported

of reactions. The national figures agree with those based on prescribing habits at the Maudsley Hospital, suggesting that tranylcypromine is more likely than phenelzine to cause hypertensive reactions with amine-containing foods. Furthermore, the dosage of phenelzine in the patients was often higher than in the controls, and duration of treatment before a hypertensive attack was longer. In one patient taking phenelzine who ate Marmite without ill-effects, hypertension was produced after doubling the usual therapeutic dose of phenelzine to 30 mg. t.d.s. Experiments in pithed rats, using a wide dose range of different amine oxidase inhibitors, indicated that tranylcypromine was more potent than phenelzine in facilitating absorption of tyramine from the intestine (Blackwell and Marley, 1966a).

(*b*) *Duration of treatment*

Prolonged treatment might predispose to hypertension due to amines in food either by increasing the tissue stores of catecholamines or by cumulative enzyme inhibition.

(*i*) *Catecholamines stores:* Tyramine raises the blood pressure by releasing noradrenaline from stores in the sympathetic nerve terminals. Treatment with a monoamine oxidase inhibitor might be expected to increase the amount of noradrenaline in nerve terminals and consequently available for release by tyramine absorbed from food, so determining the size of blood pressure response. The evidence is against this as a major factor. Urinary catecholamine concentrations following a hypertensive attack were normal in three patients; similar findings have been reported (Bass, 1961; Aldridge and Oakley, 1961; Mann and Laing, 1963). The short duration of treatment preceding hypertensive attacks in some patients and maximal potentiation of the pressor actions of tyramine after one or two doses of amine oxidase inhibitors in rats (Blackwell and Marley, 1966a) suggest that the hypertensive effects are not primarily dependent on elevated tissue amine stores. In support is the occurrence of sympathomimetic effects with cheese or yeast extracts in cats (Blackwell and Marley, 1964, 1966a, b) a species in which the noradrenaline stores are not increased by amine oxidase inhibitors (Euler and Hellner-Bjorkman, 1955).

(*ii*) *Cumulative enzyme inhibition:* Repeated therapeutic doses of monoamine oxidase inhibitors might have cumulative effects since they combine irreversibly with amine oxidase. This was shown in patient 2 when the blood pressure response to yeast extract increased with the duration of treatment. Tests on this patient also demonstrated that the blood pressure response depended upon the size of the antecedent dose of enzyme inhibitor and on the interval before ingestion of food. Patient 1, who had taken tranylcypromine for 18 months, with presumably maximal stores of amines, failed to respond to yeast extract when the last dose of inhibitor was given 18 hours before the test. This suggested that not only is enzyme inhibition cumulative but a proportion of enzyme activity recovers rapidly.

The findings accord with those from other studies in man and animals. Levine and Sjoerdsma (1963) obtained specimens of intestinal mucosa with an oral biopsy capsule from volunteers taking an amine oxidase inhibitor. They found a high rate of recovery of the intestinal enzyme within 18 hours of the last dose of drug. Natoff (1965) studied the inhibition of monoamine oxidase in mice after a single oral dose of tranylcypromine. Intestinal enzyme inhibition was maximal in 1 to 2 hours, but with 80 per cent. recovery by 4 hours when activity of the liver enzyme was only 32 per cent. of normal.

(c) Other pharmacological effects of inhibitors

Another reason for the frequent incrimination of tranylcypromine and phenelzine might be that they possess pharmacological properties other than the ability to inhibit monoamine oxidase. Phenelzine and tranylcypromine are closely related chemically to phenylethylamine and to amphetamine, drugs which raise the blood pressure by releasing noradrenaline. It is possible, therefore, that an amine oxidase inhibitor partly potentiates the pressor effects of tyramine by summation of their pressor activities. This happens in animals given large intravenous doses of the drugs (Blackwell and Marley, 1966a), but is unlikely in patients given smaller oral doses of the inhibitors which do not affect blood pressure.

The incrimination of tranylcypromine in so many of the reactions would seem to be due to a combination of wider usage and greater ability to inhibit intestinal monoamine oxidase. The different amine oxidase inhibitors vary in their effects on the enzyme in different tissues (Horita and McGrath, 1960), and further work is necessary to show whether tranylcypromine is particularly effective at inhibiting the gut and liver monoamine oxidase in man. Such a study might reveal an inhibitor effective on brain, but not gut monoamine oxidase, safer for patients to use.

C. *Variables in Dietary Factors*

(a) Individual diet: Cheese and yeast extracts are common in the diet of vegetarians and of persons with poor appetite or on weight-reducing or high-protein diets. Nearly half the patients in this series fell into one or other of these categories. The size and fat content of a meal could be important, since tyramine is not absorbed from the stomach after an amine oxidase inhibitor (Blackwell and Marley, 1966a) and individual differences in gastric emptying time and intestinal absorption would modify the rate of amine absorption.

(b) Food composition: Because there are many different varieties of cheese and yeast extract, and their effects in man and animals are so variable after amine oxidase inhibition, it is essential to know more about their amine content.

(i) Cheese

Horwitz *et al.* (1964) found up to 1·42 mg. per g. of tyramine in different cheeses and showed that as little as 6 mg. was sufficient to raise the blood pressure during treatment with an amine oxidase inhibitor. Assuming that 25 mg. tyramine would provoke severe hypertension and that 50 g. (about 2 oz.) is an average portion of cheese, only 4 out of 14 samples of Cheddar cheese analysed contained this amount, and 2 had caused hypertensive crises in patients (Blackwell and Mabbitt, 1965). Patients must be warned to avoid all cheese, since its amine content cannot be predicted from its appearance, flavour or variety, although in general unmatured "cottage" style cheeses contain less tyramine. This sort of cheese is more commonly eaten in the U.S.A. and may account for the fewer cases of hypertensive crisis reported there.

(ii) Yeast extracts

Only Marmite, of 5 different yeast extracts tested, contained large amounts of tyramine (Blackwell, Mabbitt and Marley, unpublished). Three different samples contained between 1 and 1·6 mg. per g. extract. About half a teaspoonful (5 g.) dissolved in water as a beverage would therefore contain sufficient tyramine to cause hypertension, but other yeast extracts, and Marmite, spread on bread, would probably contain insufficient tyramine.

D. *Summary of Variables*

The best way of summarizing the effects these variables have on a patient who eats cheese or other amine containing foodstuff when taking a monoamine oxidase inhibitor is to recapitulate the likely sequence of events, as shown in Fig. 3.

The patient would most commonly eat Cheddar cheese. Only about one in three or four pieces would contain much tyramine (0·5 mg./g. cheese or over), depending upon the protein content and extent to which its constituent amino-acids (e.g. tyrosine) had been converted to amines by enyzmic proteolysis or bacterial decarboxylation during manufacture.

Effects of the constituent amines would depend on the amount of cheese eaten, what else was taken, when the cheese was consumed

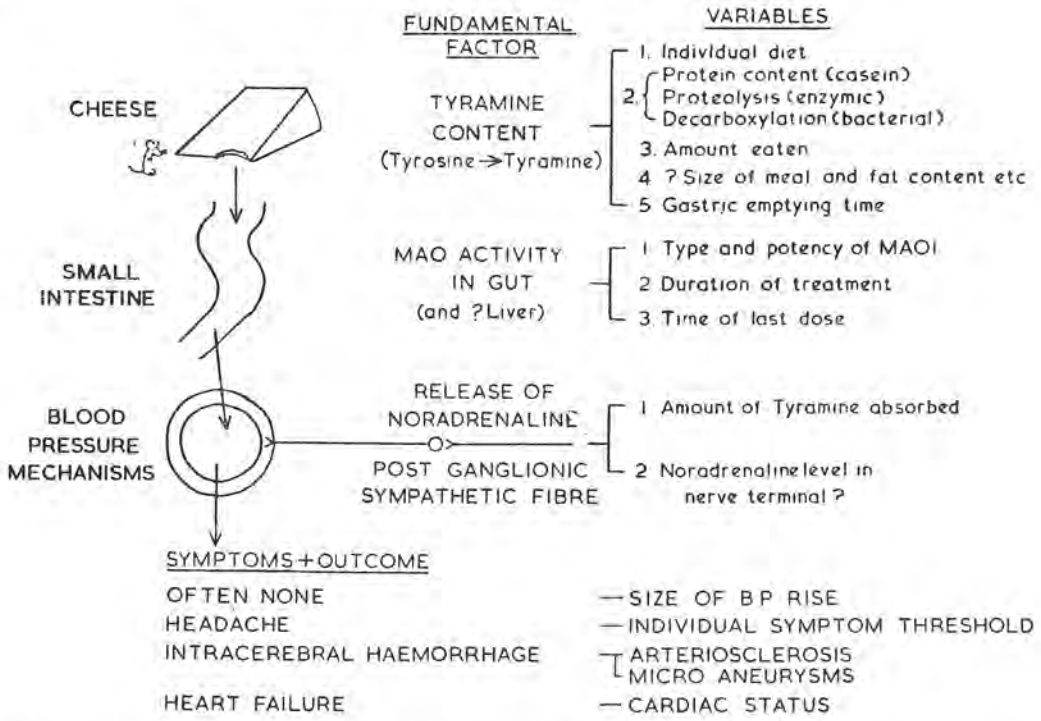

FIG. 3.—Diagrammatic representation of variable factors which determine effects caused by cheese in patients treated with a monoamine oxidase inhibitor.

in the meal and how rapidly the stomach emptied. In the uncommon event of a large amount of tyramine arriving in the duodenum during a short period of time, absorption would depend on the degree of inhibition of intestinal (and possibly liver) monoamine oxidase. If the patient had been taking an effective inhibitor (e.g. tranylcypromine) for a sufficient period, and had taken the last dose soon enough before the meal, tyramine would pass into the systemic circulation. The resulting rise in blood pressure would depend upon the amount of tyramine in the blood and possibly on that of noradrenaline in the sympathetic nerve fibres.

In the majority of cases the patient would remain symptom-free. If however, the rise in blood pressure was large, he would experience a sudden severe and characteristic headache at a critical, but individually variable, point at or above 200 mm. Hg systolic pressure. In most cases the headache and hypertension would subside rapidly before a doctor could be called, but in the rare event of a doctor being present, the patient's complaint might even then be attributed to anxiety or hysteria. In a very few cases, the rise in blood pressure would lead to heart failure or intracerebral bleeding, particularly if there were any microaneurysm or arteriosclerosis, and the patient would then be referred to a cardiac or neurosurgical unit.

CONCLUSIONS

(1) 4·3 per cent. of patients prescribed monoamine oxidase inhibitors for depression at the Maudsley Hospital between January 1963 and June 1964 experienced sudden hypertensive attacks accompanied by a severe throbbing headache. The features of the syndrome have been studied in 25 patients, of whom four

suffered an intracerebral haemorrhage and one died. Reasons are given for the delay before this condition was more widely recognized.

(2) Attacks were not due to drug idiosyncrasy as previously suggested, but were provoked by ingestion of certain foods. 17 patients had eaten cheese, and 2 had consumed a yeast extract, Marmite within 2 hours of the attack. Tests in 2 patients confirmed the association between Marmite and hypertension.

(3) Many patients ate cheese or Marmite before and after the hypertensive attacks without ill-effects. An examination was made of factors in the individual patient, the treatment and the composition of foodstuffs which might influence susceptibility.

(*a*) *The patient:* Comparisons between subjects and a control group of 50 hospital patients taking monoamine oxidase inhibitors showed that liability to hypertensive attacks was unrelated to age, sex, personality or predisposition to headache. Isoniazid clearance tests in 7 patients showed that individual susceptibility was unconnected with rate of drug acetylation. The threshold at which headache appeared during hypertension differed between patients and rises of up to 70 mm. Hg systolic pressures were sometimes asymptomatic. The number of patients experiencing such a rise in blood pressure during treatment with monoamine oxidase inhibitors may be much higher than previously supposed.

(*b*) *The treatment:*

i. The incidence of hypertensive attacks due to food substances in hospital patients treated with tranylcypromine was five times higher than in those taking phenelzine, and the difference could not be accounted for by the extent of their use. The increased risk associated with tranylcypromine is supported by national prescribing figures and by results from animal experiments. The increased risk is probably due to the drug's efficiency at inhibiting intestinal monoamine oxidase, and not to its amphetamine-like properties.

ii. Tests on the blood pressure of two patients given yeast extracts under controlled conditions, suggest that intestinal monoamine oxidase was cumulatively inhibited but recovered rapidly. The blood pressure effects of amines in foodstuffs were probably determined by these factors rather than by raised tissue catecholamine levels, since V.M.A. excretion in three patients was normal.

(*c*) *The foodstuff:* Previous publications have shown that cheese and yeast extracts vary considerably in their tyramine content, which cannot be safely predicted by appearance, flavour or method of manufacture. Cheddar cheese is usually responsible for the hypertensive crises, but only 4 out of 14 samples tested contained sufficient tyramine. Marmite contains more tyramine than other yeast extracts, but sufficient quantities are only likely to be consumed as a beverage.

(4) A brief consideration of the historical and discarded concept of alimentary toxaemia and of other relevant facts suggests that the hypertensive crisis and its precipitation by cheese and other foodstuffs could have been anticipitated before the introduction of monoamine oxidase inhibitors into clinical medicine.

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