Hypolipaemic drugs and coronary heart disease

A. N. HOWARD

From the Department of Medicine, University of Cambridge

Our knowledge of lipid metabolism has expanded enormously during the last 15 years, much of this being due to advances in separation techniques—electrophoresis, ultracentrifugation, nephelometry, thin-layer and gas chromatography. In consequence the analysis of the major lipids, particularly the plasma lipoproteins, has reached a high degree of complexity and refinement. Because of the possible implications of hyperlipaemia in the aetiology of atherosclerosis, especially coronary heart disease, the pharmaceutical industry has been very active in this field and a number of drugs are currently available for lowering elevated blood lipids. So far there is no one drug which will effectively lower serum lipids in all cases. Thus an important feature of treatment is the correct diagnosis before therapy of the type of lipoprotein abnormality.

A major question is whether any benefit can be derived from lowering blood lipids. Evidence is presented which supports the association between elevated blood lipids and the incidence of coronary heart disease. However, it is not experimentally established with any certainty that the procedure of lowering lipids is of any positive benefit in patients who have developed coronary heart disease or even in healthy symptomless patients. This review examines the rationale behind the diagnosis and drug treatment of the hyperlipoproteinaemias, and summarizes the current status of their usefulness in the treatment of coronary heart disease.

Serum Lipids as Risk Factors in Coronary Heart Disease

The evidence that hyperlipaemia is one of the factors involved in coronary heart disease is very impressive. One of the most important studies is that carried out in Framingham, Massachusetts (Gordon and Verter, 1969). Over 5000 men and women aged 30-62 were studied for over 12 years in a prospective study. A clear-cut linear relationship between serum cholesterol and new coronary events was established. Thus, the chance of a man of 40 developing coronary heart disease with a serum cholesterol of 300 mg/100 ml is three times greater than one with 200 mg/100 ml.

It is commonly suggested that the Framingham data indicate that a raised serum cholesterol concentration is not important over the age of 65 because the percentage risk is much higher in men at 40 than at 65 (fig 1). However, in absolute terms, the numbers of men dying per year is actually greater at 65, and the absolute difference in death rate between men with a serum cholesterol level of 300 mg/100 ml and 200 mg/100 ml is very much greater than at 40 years (Dayton, 1972). Further prospective studies carried out at five other centres in the USA confirm the Framingham result (Stamler, 1967).

The situation regarding triglycerides has been obscure until quite recently because of the lack of a clear-cut prospective study. However, Carlson and Bottiger (1972) in a nine-year follow up of 3168 men in Stockholm showed that coronary heart disease increased linearly with increasing fasting concentrations of plasma triglycerides, and that the risk was independent of plasma cholesterol. A combined elevation of these two plasma lipids carried the highest risk (table I).

Hyperlipoproteinaemia

Cholesterol and triglycerides circulate in the blood as complex lipoproteins and these have been classified according to their separation by electrophoresis or ultracentrifugation (fig 2) into high density (HDL), low density (LDL), very low density (VLDL) and chylomicrons. As the particles increase in size they contain relatively more triglyceride and less cholesterol.

Fredrickson, Levy, and Lees (1967) proposed the separation of familial abnormalities into five types (table II). However, it is important to note that this original classification concerned genetic lipoprotein abnormalities and did not include a cross section of cases found in a 'normal' population. Based on a Fredrickson classification, the World Health Organisation (Beaumont, Carlson, Cooper, Fejfar, Fredrickson, and Strasser, 1970) recommended a separation of type II into type IIa, in which there is pure hypercholesterolaemia, and type IIb in which both
Hyperlipaemic drugs and coronary heart disease

**NOMENCLATURE**

<table>
<thead>
<tr>
<th>Electrophoresis</th>
<th>α</th>
<th>β</th>
<th>pre-β</th>
<th>origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flotation Sf</td>
<td>&lt;0</td>
<td>0 - 20</td>
<td>20 - 400</td>
<td>&gt; 400</td>
</tr>
<tr>
<td>Light Scattering Particles</td>
<td>S</td>
<td>M</td>
<td>L</td>
<td></td>
</tr>
<tr>
<td>Composition</td>
<td>Constant Cholesterol</td>
<td>Variable Triglyceride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Fig 1** Nomenclature, composition and size of serum lipoproteins.

<table>
<thead>
<tr>
<th>Group</th>
<th>Serum Cholesterol</th>
<th>Rate CHD/10³/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal (280 mg/100 ml)</td>
<td>7.3</td>
</tr>
<tr>
<td>2</td>
<td>Raised (170 mg/100 ml)</td>
<td>15.6</td>
</tr>
<tr>
<td>3</td>
<td>Normal (250 mg/100 ml)</td>
<td>26.8</td>
</tr>
<tr>
<td>4</td>
<td>Raised (300 mg/100 ml)</td>
<td>31.3</td>
</tr>
</tbody>
</table>

**Table I** Risk of developing coronary heart disease in relation to serum cholesterol and triglycerides (Carlson and Bottinger, 1972)

**Fig 2** Incidence of coronary heart disease at ages 40 and 65 in Framingham study (Dayton, 1972).

Hypercholesterolaemia and hypertriglyceridaemia are present such that there is an increase in both LDL and VLDL (table II).

In addition, Stone, Thorp, Mills, and Dick (1971) used a method of analysis which separated the lipoproteins by means of their size (table II), simply calling chylomicrons—large (L), VLDL—medium (M) and LDL—small (S). These two classifications now accommodate all types irrespective of whether the condition is inherited or acquired.

Differentiation of the types is usually accomplished by estimations of total cholesterol and triglyceride and either electrophoresis or nephelometry. In the case of type III disease an abnormal (floating-beta) lipoprotein is present, seen as a 'broad-beta' band by electrophoresis. This type can be confirmed only by preparative ultracentrifugation.

In the severely affected untreated forms all the types of hyperlipoproteinaemia give rise to xanthomas, and coronary heart disease is a feature for all except type I (Fredrickson, et al, 1967). The commonest types are IIa, IIb and IV, the last being the most common; type I is very rare (Fredrickson, 1971).

Hyperlipoproteinaemias can occur as complications in a number of diseases. It is important to exclude pancreatitis, diabetes, hypothyroidism,
obstructive liver disease, the nephrotic syndrome, hepatic disease, dysglobulinæma, glycogen storage disease, multiple myeloma, alcoholism and pregnancy before establishing a diagnosis of primary hyperlipoproteinaemia.

**Drugs Commonly Used in Treatment of Hyperlipoproteinaemia**

Drugs can affect lipid metabolism in a number of ways. For reduction of serum cholesterol they may inhibit synthesis or increase elimination of cholesterol as faecal steroids or redistribute cholesterol between plasma and tissues. For reduction of triglycerides they can decrease synthesis or increase utilization. Table III gives the mechanism of action of the main types of drugs commonly employed. Not every drug is effective against the different types of hyperlipoproteinaemia, and their potency is listed in table IV, together with some important side effects.

**CLOFIBRATE**

This is the most widely used drug for the treatment of hyperlipaemia (Oliver, 1967). In the rat, clofibrate has a pronounced effect on serum cholesterol but...
in man its chief effect is on triglycerides. Many mechanisms of action have been proposed. Its effect on serum triglycerides is thought to be due to the increase of liver α-glycero phosphate dehydrogenase, an enzyme involved in triglyceride metabolism (Pereira and Holland, 1970). However, the diminution of plasma free fatty acids and enhanced triglyceride utilization cannot be ignored (Steinberg, 1970).

The drug is chiefly of use in those lipoprotein abnormalities in which VLDL is elevated (Friedrickson, 1971). Its efficacy in type III is dramatic and almost diagnostic of the disease. In view of its pronounced effect on cholesterol metabolism it is curious that the drug is usually ineffective in type IIa. An important side-effect of treatment is an increase in the incidence of gallstones (Coronary Drug Project, 1975).

ANION-EXCHANGE RESINS
This class of drug acts by combining with bile acids in the intestine, thereby facilitating their increased excretion (Bergen and Van Itallie, 1963). Since bile acids are synthesized from cholesterol in the liver, the body content of cholesterol is decreased providing a large enough dose is used. Unfortunately, the liver compensates by synthesizing more cholesterol from acetate, and the total effect on serum cholesterol is often disappointing.

The first anion-exchange resin to be utilized was cholestyramine (Van Itallie and Hashim, 1963), and was presented as a gritty powder with an unpleasant fishy odour. More recent preparations are an improvement. Other resins now available are colestipol (Miller, Clifton-Bligh, Nestel, and Whyte, 1973) and Secholex (Howard and Hyams, 1971; Courtenay Evans, Howard, and Hyams, 1973), the latter having the advantage of being a smooth, tasteless gel. Colestipol (Clifton-Bligh, Miller, and Nestel, 1974), and in some cases cholestyramine (Weizel, Estrich, Splitter, Pomeroy, and Kinsel, 1969; Grundy, Ahrens, and Salen, 1971), increases serum triglycerides, a serious disadvantage. (There are no reports of Secholex having similar action.) The reason is not clear but chenodeoxycholic acid is involved in triglyceride metabolism (Miller and Nestel, 1974), and some anion exchange resins may preferentially sequester this bile acid.

The side-effects of the resins are purely gastrointestinal since they are not absorbed. Constipation, which occurs in about 20% of patients, can be treated with suitable laxatives.

D-THYROXINE
The rationale behind the use of this compound is that L-thyroxine is markedly hypcholesterolaemic, for example, in myxöedema where the serum cholesterol level is raised. The dextro-isomer still possesses hypcholesterolaemic activity (Starr, Roen, Freibrum, and Schleissner, 1960; Oliver and Boyd, 1961a) but is a less potent metabolic stimulant. Its exact mode of action is uncertain but faecal neutral steroids are increased (Miettinen, 1970). There is a moderate increase in degradation of cholesterol to bile acids but also a compensatory rise in cholesterol biosynthesis. It is most useful in type IIa.

The side effects are related to its mild metabolic stimulatory action, and it is generally not recommended for patients with preexisting cardiovascular disease. Symptoms of angina are exacerbated. However, these difficulties can be circumvented by combining the drug with a β-adrenergic blocking agent, such as propranolol (Krikler, Lefevre, and Lewis, 1971).

NICOTINIC ACID
This is one of the first compounds shown to have hypolipaemic activity (Altschul, Haffer, and Stephen, 1955; Parsons, 1961), and yet its most important mechanism of action is still unclear. Like clofibrate, it increases the faecal output of neutral steroids and depresses cholesterol biosynthesis (Miettinen, 1970). It decreases serum triglycerides, possibly by its effect on fatty acid incorporation into adipose tissue. Its greatest potential use is in the treatment of those hyperlipoproteinaemias with elevated triglycerides, its action in type IIa being significant but somewhat less than the other types (Carlson and Orö, 1973).

Its grave disadvantage is the side effect of peripheral vasodilatation (flushing) which many patients find initially disturbing. Also it often produces gastrointestinal discomfort, hyperuricaemia and hyperglycaemia. Attempts to modify the side effects by a change in chemical constitution have not been too successful since the action of the drug is dependent on the free nicotinic acid form. β-Pyridylcarbinol (Gaut and Taylor, 1968) and pentaerythryl nicotinate (Harthon and Svedmyr, 1974) are claimed to offer some improvement and fewer side effects.

NEOMYCIN
This antibiotic, which is chiefly unabsorbed in the gastrointestinal tract, is a potent hypcholesterolaemic agent (Samuel, Holtzman, and Goldstein, 1967). Its mode of action is to inhibit the formation of fat micelles in the intestine, leading to malabsorption of fat and increased excretion of neutral and acidic sterols (Thompson, Barrowman, Gutierrez, and Dowling, 1971). Despite these properties, which are particularly useful in treating type IIa, the compound has not achieved widespread use. This
could be related to its major side effect of audio toxicity (Gibson, 1967; Greenwood, 1959; Halpern and Heller, 1961; Greenberg and Momary, 1965; King, 1962). Neomycin, if absorbed in quantity, can cause permanent deafness with oral treatment (several cases have been reported). Analogues, eg, methyl neomycin, have been developed but not widely used (van den Bosch and Claes, 1967).

OESTROGENS
The rationale behind their use is that coronary heart disease in premenopausal women is much less common than in men. Of those investigated, conjugated equine oestrogens (Premarin) have been the most widely used (Stamler, Pick, Katz, Pick, Kaplan, Berkson, and Century, 1963). The mechanism of action is to alter liver lipoprotein production such that HDL cholesterol is increased and LDL cholesterol decreased. However, there is a compensatory rise in VLDL triglyceride (Furman, Alaupovic, Bradford, and Howard, 1968). It is only weakly hypocholesterolaemic and of use in patients moderately affected with type IIa. Side effects are those of oestrogens—feminization, particularly gynecomastia, in men. It is not recommended immediately after acute myocardial infarction since an excess of sudden deaths has been reported (Stamler et al, 1963).

COMBINATION OF ANION-EXCHANGE RESINS WITH CLOFIBRATE
There is no potent single compound for lowering raised levels of LDL as seen in type IIa, a decrease of 15-20% in serum cholesterol being all that can normally be achieved even with large doses of the above-mentioned drugs; such a fall is often insufficient to reduce the cholesterol level to normal. With a combination of clofibrate and Secholex, decreases of 30-40% in serum cholesterol are possible (Howard and Hyams, 1971; Courtenay-Evans, Howard, and Hyams, 1973). Figure 3 illustrates the treatment of five type IIa patients resistant to clofibrate.

The combination of the two drugs acts synergistically. Clofibrate inhibits liver cholesterol biosynthesis (Grundy, Ahrens, Salen, Schrieberman, and Nestel, 1972) and increases the excretion of biliary acid bilirubins (Horning, Herbert, Roth, Davis, Horning, Fischer, and Jourdan, 1972). Both of these properties would enhance the action of anion-exchange resins (fig 4). The combined effects of clofibrate with either cholestipol (Fellin, Baggio, Balestrieri, Briani, Balocchi, and Crepaldi, 1974) or cholestyramine (Olsson, Carlson, and Rossner, 1974) are not so striking as those with Secholex.

Another explanation of the combined action of resins and clofibrate is that different lipoproteins are affected. Clofibrate is very effective in reducing the level of VLDL in type IIb but also increases the action of Secholex on LDL in type IIa (Howard and Courtenay-Evans, 1974). Since cholestipol and cholestyramine increase VLDL, a combination of these resins with clofibrate is also an advantage.

OTHER COMBINATIONS OF DRUGS
Theoretically it is possible to combine all these individual drugs and obtain improvements in efficacy. Among those which have been tried with success are cholesterol and nicotinic acid (Berkowitz, 1965; Moutafis, Myant, Mancini, and Oriente, 1971); clofibrate and neomycin (Samuel,
Holtzman, Meilman, and Sekowski, 1970); D-thyroxine and clofibrate (Strisower, 1966; Best and Duncan, 1966); and D-thyroxine and nicotinic acid (Kuo and Bassett, 1963).

Dietary Restriction

All the drugs I have mentioned will be effective without modification of the diet. In some patients, dietary restriction alone is very effective; in others it is disappointing. A combination of dietary restriction and drug treatment is invariably superior to each given separately. For completeness, table V shows the type of dietary treatment which is used in the various types of hyperlipoproteinaemia (Fredrickson, 1971; Fredrickson, et al., 1967). To summarize, raised LDL is treated with a polyunsaturated low-saturated-fat and low-cholesterol diet; raised VLDL with carbohydrate restriction, and raised chylomicrons by restricted total fat intake. When the patient is obese a reduced calorie diet is advocated, and when fat and carbohydrate are both restricted, a high-protein diet is used.

The mechanism by which polyunsaturated fats decrease serum cholesterol levels is still subject to debate. Recent evidence suggests that the main effect is to redistribute cholesterol between plasma and tissues rather than to remove it from the body (Grundy and Ahrens, 1970).

Value of Lowering Serum Lipids

Drug Studies

There is as yet no conclusive evidence that lowering serum lipids by drugs is a worthwhile preventative measure against cardiovascular disease. The chief reason for this is that it is only during the last 10 to 15 years that potent hypolipaemic drugs have been available. Since the protocol of any trial requires large numbers of subjects, many years of treatment, and is expensive, it is not surprising that there is a paucity of results.

Table V Dietary restriction in the various types of hyperlipoproteinaemia

<table>
<thead>
<tr>
<th>Type of Hyperlipoproteinaemia</th>
<th>Restricted* Fat</th>
<th>Modified* Fat</th>
<th>Restricted* Cholesterol</th>
<th>Restricted* Carbohydrate</th>
<th>Restricted* Alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>IIa</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>IIb</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>III</td>
<td>± 1</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>IV</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*25-35 g/day
*High in polyunsaturated and low in saturated fatty acids
*About 100 mg/day
*1-5.4-0 g/kg
*1-5.3-0 g/kg

Early work by Stamler et al (1963) with conjugated equine oestrogens (Premarin) gave an encouraging result. In 275 patients, the five-year mortality was reduced by 50%. However, mortality with this preparation was increased during the early acute stage of myocardial infarction. In contrast, Oliver and Boyd (1961b) found that another oestrogen, ethinyl oestradiol, was ineffective. Thus the significance of oestrogens in the therapy of myocardial infarction is very much in doubt, particularly as Premarin (10 mg/day) has been withdrawn from the cooperative drug study (Coronary Drug Project, 1970) because of an excess of sudden deaths. In these trials D-thyroxine was also withdrawn for similar reasons (Coronary Drug Project, 1972).

For clofibrate, the first trials published were those conducted in Edinburgh (Oliver et al., 1971) and Newcastle (Dewar et al., 1971). A total of 1214 patients with preexisting cardiovascular disease, either myocardial infarction or angina, were studied for four years. The endpoints studied were sudden death, fatal and non-fatal myocardial infarction. The results were in some ways disappointing. Of 620 patients treated with clofibrate (2 g/day), 79 (13%) died of sudden death or myocardial infarction compared with 59 (10%) in the placebo group. This is not a very striking difference. Table VI shows the results in the Edinburgh trial only, which is representative of both trials. Among those suffering from angina only, clofibrate had a statistically beneficial effect in reducing mortality. Since this was a smaller proportion of the total numbers studied, the effect is masked in the overall figures.

The reduction in events in the angina group was independent of the initial serum cholesterol and there was no correlation between the degree of lowering and protection. Clofibrate had a more pronounced effect on serum triglycerides, and also raised the levels of free fatty acids, affected fibrinolysis, and produced abnormal platelet stickiness and fibrinogen. None of these parameters were measured.
and any one of them could be important (Dewar and Oliver, 1971).

The Coronary Drug Project (1975) confirmed the lack of effect of clofibrate on mortality of patients with myocardial infarction, and also obtained a negative result with nicotinic acid. In this five-year study, which involved over 3500 patients with a previous history of myocardial infarction, the mortalities were 20·0% for clofibrate, 21·2% for nicotinic acid, and 20·9% for placebo. No patients with angina as the only symptoms were studied. Thus the hypothesis that clofibrate benefits patients with angina not having a myocardial infarct remains unchallenged. Disturbing findings with clofibrate were a statistically significant excess incidence of thromboembolism, angina pectoris, intermittent claudication and cardiac arrhythmia as well as a two-fold increase in the incidence of gallstones.

Another trial, presented as a preliminary report only, has given a positive result. In the clinical pharmacology trials of colestipol (Dorr, Martin, and Freyburger, 1974) some 2000 patients were studied for over three years. Of these, 500 had pre-existing myocardial infarction, and were randomly distributed between treatment with placebo and drug (table VII). The number of deaths was greatly reduced in the drug-treated group, especially those from coronary heart disease. The drug had no effect on non-fatal coronary events. Whilst this result is extremely encouraging, no evaluation can be made until the protocol and results are published in detail.

**EFFECT OF DIET**

Two trials which have examined the effect of a prudent diet (high polyunsaturated, low saturated fat and low cholesterol) on the morbidity and mortality of patients with coronary heart disease have given equivocal results. In a trial in Oslo, Leren (1966) found that in 412 subjects lowering serum cholesterol by 14% did not affect the incidence of sudden deaths. However, the number of coronary events were significantly reduced (table VIII). Likewise in a trial with 373 patients, in which soya bean oil was employed, the difference in serum cholesterol between experimental subjects and controls was 16% and no difference in death rate was established (Morris et al, 1968).

<table>
<thead>
<tr>
<th>Type of Prevention Trial</th>
<th>Place</th>
<th>Total No. of Subjects</th>
<th>Serum Cholesterol</th>
<th>No. of Deaths from Coronary Heart Disease</th>
<th>No. of Subjects with Relapses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>New York¹</td>
<td>941</td>
<td>457</td>
<td>225</td>
<td>250</td>
</tr>
<tr>
<td></td>
<td>Helsinki²</td>
<td>313</td>
<td>241</td>
<td>217</td>
<td>268</td>
</tr>
<tr>
<td></td>
<td>Los Angeles³</td>
<td>424</td>
<td>422</td>
<td>186</td>
<td>232</td>
</tr>
<tr>
<td>Secondary</td>
<td>London⁴</td>
<td>194</td>
<td>199</td>
<td>221</td>
<td>258</td>
</tr>
<tr>
<td></td>
<td>Oslo⁵</td>
<td>206</td>
<td>206</td>
<td>239</td>
<td>283</td>
</tr>
</tbody>
</table>

Table VIII  
*Effect of diet on mortality from coronary heart disease*

¹Christakis et al (1966)  
²Turpeinen, Miettinen, Karmonen, Poine, Pekkarinen, Lehtosuo, and Alivirta (1968)  
³Dayton, Pearce, Hashimoto, Dixon, and Tomiyasu (1969)  
⁴Morris et al (1968)  
⁵Leren (1966)  
*No significant difference in total deaths.
Hypolipaemic drugs and coronary heart disease

There have been several trials in which a prudent diet has been examined as a prospective study in healthy populations. Whilst the incidence of coronary events has been statistically reduced, the overall effect on mortality was not striking. Table VIII shows the results of three trials in New York, Helsinki and Los Angeles. First, the mean difference in serum cholesterol achieved by diet was not large, being 25-50 mg (10-15 %).

A clear-cut and statistical reduction in deaths from coronary heart disease was achieved only in the Los Angeles trial but overall mortality was not affected, there being more deaths from cancer in the experimental group.

The general conclusion from all these trials is that further work in several thousands of subjects over many years would be necessary to provide a conclusive answer as to whether lowering serum lipids by diet can affect mortality from coronary heart disease.

Advisability of Treatment

In the light of current knowledge, most physicians are of the opinion that hyperlipoproteinaemia should be treated, irrespective of the current status of clinical trial results. In the case of severely affected patients, especially those with xanthoma, and those in whom there is a high familial risk of coronary heart disease, the decision is clear. However, the mass of the general population who may be mildly hyperlipaemic presents a different problem. The minimum requirement for the use of a drug in these people is that it should not be toxic and be relatively free of unpleasant side effects. Another question is that of expense since chronic drug treatment is not cheap. Some would advocate a modification of the diet as a first step, followed by drug treatment if unsuccessful. However, the mechanism of action of most of the drugs mentioned above is to remove cholesterol from the body rather than cause its redistribution, as is the case for a polyunsaturated fat diet. Such a consideration might be of primary importance in the ability to effect a reduction of deposited cholesterol in atherosclerotic plaques.

There are a number of long-term trials now in progress to evaluate hypolipaemic drugs, especially the anion exchange resins (Ahrens, personal communication). Results of these are awaited with great interest because they will largely decide who is to be treated, and whether the prevention of coronary heart disease is within the realms of possibility.

References


Coronary Drug Project (1972). Findings leading to further modification of its protocol with respect to Dextrothryoxine. J. Amer. med. Ass., 220, 996-1008.


