Ecogenetics

— J Op't Hof

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Summary

Some of our patients are high-risk individuals because of their genetic make-up. This article helps the GP to understand ecogenetics and pharmacogenetics better, why a screening programme has been instituted and how every GP has a contribution to make in this field.

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KEYWORDS: Genetics; Pharmacogenetics; Genetic screening; Environment

Curriculum vitae

Johann Op't Hof matriculated at the Afrikaanse Hoërseunskool in 1957 after which he attained a BSc degree at the University of Stellenbosch in 1962. In 1966 a BSc (Hons) degree and in 1968 a MSc degree were completed at the University of Pretoria. Thereafter a DSc degree in Human Genetics was completed at the University of Freiburg in Germany. In 1971 Johann Op't Hof assumed and still holds the post as Head of Genetic Services in the Department of National Health and Population Development. A MSA degree (Masters in State Administration) was attained at the University of Pretoria in 1981. He is a member of several scientific associations and author of several books on genetic services in the RSA. More than 90 scientific articles have been published.

Every species, including man, owes its survival to the genetic variability with which it is endowed. Fortunately no two individuals, except identical twins, are genetically alike. It is precisely this variability which affords a population with the ability to adapt and survive the changing environment. Through the interaction between the environment and specific genotypes of the organism, the eventual phenotype is expressed.

This principle is fundamental to classic genetic theory and applies to the genetics of all living organisms, including man. The continuous source of genetic variability is provided by a steady state of mutational load which a population acquires over decades and centuries. Well-known examples include the genetically determined variation of blood groups, plasma proteins, tissue incompatibility, immune systems and other products of genes and gene action of the cell[1].

As much as mutations can be beneficial on the one hand, they may equally be detrimental in certain environments on the other hand. Very often a mutation, ie a change in the DNA which is passed on from one generation to the next, is directly recognisable as a disease or genetic disorder, such as haemophilia, porphyria or albinism[2].

There are also mutations which give rise to a variant of an existing gene without any clinically observable effect under "normal" environmental circumstances. Certain environmental circumstances may, however, prevail which ellicit an abnormal and even detrimental effect of a specific genetic variant[3]. Man's differential reaction to drugs, is a classic illustration of how genetic variation finds expression under certain conditions. This phenomenon is fundamental to the concept of what is today generally known as pharmacogenetics[4,5,30]. Extending the concept of man's differential response and reaction to drugs to prescribe the differential susceptibility to environmental agents in general, gave rise to the concept of *ecogenetics* as recently as the 1970s[6].

Pharmacogenetics

When Vogel coined the term pharmacogenetics in 1959[3], a well-known phenomenon became entrenched in an interdisciplinary area shared by pharmacology and human genetics, namely genetically determined variation in man's reactions to

drugs and the precipitation or aggravation of genetic disorders by drugs.

The haemoglobinopathies have become the classic example to demonstrate the role of mutations in the origin and existence of inter-individual biochemical variation. Landmarks in scientific endeavours illustrating this relationship and the role of mutations include the demonstration of Pauling *et al*[7] (1949) that sickle-cell anaemia is related to a genetically determined biochemical disorder.

G6PD Variation

It was particularly Motulsky who in 1957, demonstrated that the inter-individual biochemical genetic variability of the enzyme, glucose-6-phosphate dehydrogenase (G6PD) elicited an abnormal response towards certain drugs in persons with certain G6PD types[8].

The drug primaquine has been used in the treatment of malaria for many years. However it was found that certain individuals are particularly sensitive to the drug. After taking the drug for a few days, these patients would suddenly begin to pass a darkly coloured urine with the onset of a serious haemolytic episode which could sometimes be fatal. The primaquine sensitivity was found to be due to a deficiency in the red cell enzyme, glucose-6-phosphate dehydrogenase (G6PD).

Man's differential reaction to drugs illustrates how genetic variation finds expression under certain conditions

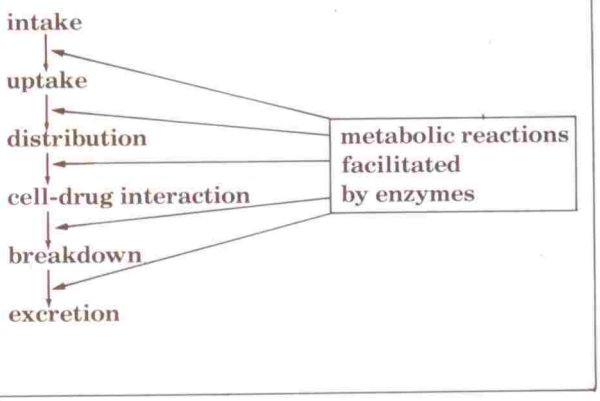
During the Korean war it was found that approximately 10% of the Black American soldiers were primaquine-sensitive as compared to approximately 0,1% in Whites. It has also been known for many years that some individuals, particularly from Mediterranean countries, are prone to a haemolytic episode after eating broad beans *(Vicia faba)* which was later established to be the result of G6PD deficiency[9,17].

Persons with G6PD deficiency have subsequently been found to be sensitive to several other compounds, such as furadantin, aspirin, phenacetin, certain sulphonamides, and naphthalene (moth balls)[4]. More recently some evidence has been presented that the susceptibility to cancer may be related to G6PD deficiency[10].

Drug metabolism

When consumed, most drugs are broken down (anabolism) before being excreted. The metabolism of the drug is characterised by a typical sequence. (See Figure 1.)

Figure 1



These steps in metabolism are facilitated by enzymatic reactions. Enzymes in turn are the direct products of genes (DNA) and protein synthesis. A mutation in the DNA will thus be reflected in a variant product eg a variant enzyme. Such a variant may result in an electrophoretically visible isozyme or enzyme variant with or without altered enzyme function[1,11]. Not all mutations can be identified as visibly discernable variants[13,14].

Many drugs undergo bio-transformation prior to excretion. It is precisely at this level that the inter-individual variation to drug response is noted.

Pseudocholine esterase deficiency

Most people have the enzyme pseudocholine esterase which is capable of breaking down the muscle relaxant succinylcholine when administered. There are, however, some individuals who do not have the normal gene for the enzyme pseudocholine esterase and instead have a variant due to a mutation. Therefore they cannot metabolise the muscle relaxant normally, with the result that the drug action persists and respiratory distress (apnoea) can set in[4,15]. Most people are homozygous for the normal allele ($E1^u/E1^u$), whereas 3-4% of caucasians are heterozygous for a defective allelic gene ($E1^u/E1^a$). The incidence of the individuals homozygous for the defective gene ($E1^a/E1^a$) is approximately 1 in 3 000[18].

The RSA is known in the medical world for the occurrence of porphyria

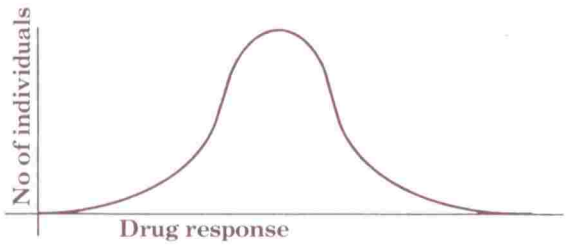
Drug response

Because differential drug response is genetically determined, variation in the response is accordingly revealed in various ways.

The variation in response may be unifactorial or

multifactorial. In the latter case several genes are involved and the distribution of the response will be unimodal or continuous, as seen in Figure 2.

Figure 2



If normal drug metabolism is governed by a dominant gene D, some people may not be able to metabolise the drug because they are homozygous for the recessive gene d. Thus three genotypes are possible, namely DD, Dd, and dd. If the responses of DD and Dd are discernable, then all three genotypes can be recognised and a trimodal distribution will be evident (see Figure 3). If DD and Dd are not discernable, only a bimodal distribution will result (see Figure 4).

Figure 3

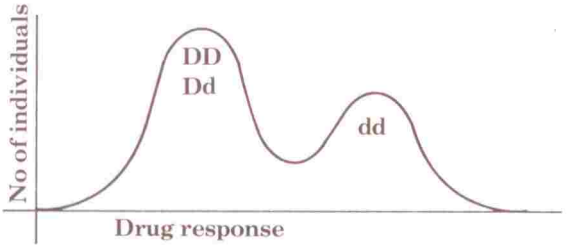
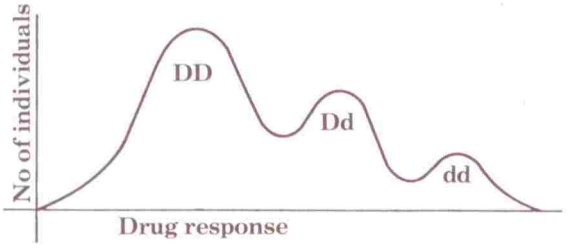


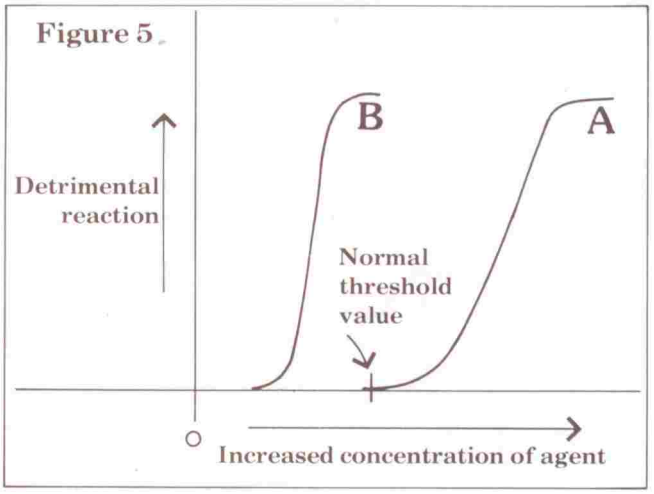
Figure 4



Another characteristic feature of ecogenetic responses is the altered threshold level at which the environmental agent precipitates a particular manifestation (Figure 5)[19].

Environmental agents will normally only have an effect on a "normal" person after a certain threshold concentration level has been reached (Figure 5 curve A). This means that the majority of people (± 98%) will not be affected below a certain critical threshold level. There is, however, a small number of individuals who, because of a specific genetic endowment, suffer from an acute reaction at a concentration far below the normal threshold level (Figure 5, curve B).

Figure 5



Variegate porphyria

One of the best examples of differential pharmacological action is demonstrated by drug responses in persons with various types of porphyria. In the medical world, South Africa is known for the occurrence of porphyria (especially variegate porphyria) - the research of which was pioneered by Dr Geoffrey Dean in the late 50s early 60s[20].

Variegate porphyria is inherited in a dominant fashion and has been known since the early settler days in the Cape as a condition which only involves sensitivity of the skin to sunlight. In later years, with the advent of modern drugs, the sufferers of variegate porphyria also exhibited unusual characteristic signs and symptoms when subjected to certain drugs such as sulphonamides, barbiturates, several anaesthetics and even alcohol. In most cases the reactions to these drugs are severe and in acute cases can be fatal[21,22].

It is estimated that one in 300 Afrikaners has the gene for variegate porphyria, an occurrence 100 times more than in any other population.[23]

Hyperlipidaemia

Familial hyperlipidaemia is a metabolic disorder and possibly one of the most frequently occurring diseases among Whites in South Africa, particularly among the Afrikaner population associated with coronary heart disease[28]. The Frederickson Type II A hyperlipoproteinaemia is the common dominantly inherited type of hyperlipidaemia amongst Whites especially Afrikaners of which one in 80 are heterozygous and approximately one in 30 000 are homozygous for this dominant gene[29,30]. Environmental factors, such as diet, are however important precipitating factors of hyperlipidaemia. Even in the ill defined genetic types of hyperlipidaemia, ranging between the multifactorial and single gene types, the genetic predisposition to manifestation is evident.

Ecogenetic reactions in general

Thus extending the principle of pharmacogenetics in conjunction with the nature and magnitude of genetic variability or polymorphism in the general population, a logical explanation for genetically determined differences in susceptibility to common environmental agents, such as chemicals, infections and physical agents can be found. This realisation led to the establishment of the term *ecogenetics* referred to earlier[1].

Examples of ecogenetic manifestations due to genetic variation in susceptibility are given in Table 1.

Specific forms of interaction between the genotype of man and the environment have been identified and described, reflecting for example the genetically determined susceptibility to mutagens, carcinogens, teratogens and common diseases[2,3].

A schematic representation of the inter-relationship between the components of ecogenetic systems is illustrated in Figure 6.

Figure 6

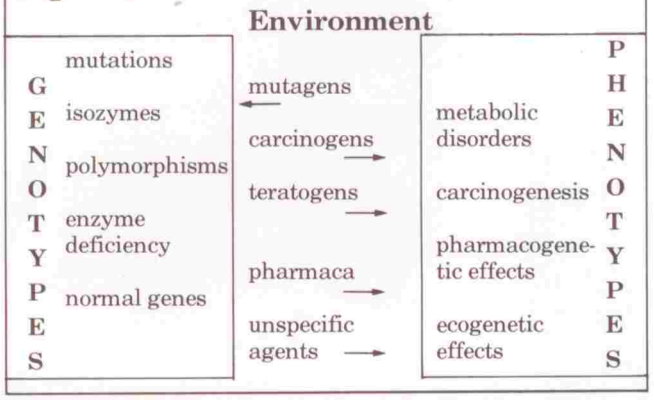


Fig 6: Diagrammatic representation of the ecogenetic interaction genotype and environment by means of which a specific phenotype becomes manifest.

Table 1: Genetic variation and ecogenetic manifestation

Environmental risk	Disorder	Manifestation
Radiation		
Ionising radiation including UV	Defective DNA repair disorders, eg xeroderma pigmentosa, Fanconi's anaemia, Bloom syndrome, ataxia telan-giectasia	Chromosome instability and breakage Skin cancer
Drugs and chemicals		
Barbiturates sulphonamides	Porphyria	Disturbed haem metabolism Accumulation of porphyrins and porphyrin precursors Acute abdominal pain and muscular paralysis
Primaquine sulphonamides aspirin, naphthalene	G6PD deficiency	Haemolytic episode
Suxamethonium, succinyldicholine	Pseudocholinesterase variation	Apnoea prolonged due to depression of respiratory muscles
INH	INH slow inactivator	Polyneuritis
Halothane	Malignant hyperthermia	Hyperthermia, Muscle rigidity
Parathion, paraxon, cholinesterase-like inhibitors	Serum para-oxonase polymorphism	Reduced toxicity
Oxidative drugs	Methaemoglobinaemia reduced deficiency	Methaemoglobinaemia Cyanosis
Thiopurines	Thiopurine methyltransferase (TPMT) variation	Leucopenia and liver damage
Air pollution		
Dust, gases, smoke	Alpha-1-antitrypsin deficiency	Emphysema
Food		
Fava beans	G6PD deficiency	Favism
Alcohol	Atypical ADH	Alcoholism
Milk	Lactose intolerance	Lactose intolerance
Fats	Hypercholesterolaemia	Atherosclerosis
Fortified flour	Haemochromatosis	Iron overload

Where the workplace is the ecogenetic risk environment, we speak of *occupational genetics*[24]. It was Haldane who in his book *Heredity and Politics* for the first time suggested in 1938, that the problem of an occupational disease "potters bronchitis" in the UK could best be approached by establishing why some potters got bronchitis and others not[25]. He implied that the bronchitis of potters could be ascribed to a genetic predisposition of inter individual susceptibility to bronchitis. Thus, although an attempt is made with traditional industrial hygiene to limit toxic substances in the workplace to a minimum, there will always be some individuals who, because of their genetic constitution, will not be able to cope with even the "safe" level of an environmental agent and the workplace will constitute a danger to them[24]. A classic example of an ecogenetic reaction where certain individuals are hypersusceptible to certain environmental agents, is serum alpha-1-antitrypsin deficiency.

Serum alpha-1-antitrypsin (SAT) deficiency

Approximately 90% of the alpha-1-globulin fraction in plasma comprises of alpha-1-antitrypsin which has the function to inhibit proteolytic enzymes. Proteolytic enzymes released by the leucocytes as well as pulmonary macrophages are harmful unless they are inhibited or regulated by SAT. SAT deficiency is determined by a recessive gene. Individuals homozygous for SAT deficiency ie 1:4000 of the population are extremely sensitive to cigarette smoke, gases and air pollution which give rise to liver cirrhosis and pulmonary emphysema and

Man owes his survival to the genetic variability with which he is endowed – it helps him to adapt to a changing environment

obstruction in these individuals. Various allelic variants of the normal gene exists, and individuals heterozygous for these alleles also exhibit various degrees of hypersensitivity to the environmental agents mentioned. Merely 10% of the population (Whites) are heterozygous for any of the allelic variants of SAT deficiency[26]. The need to identify the at risk individual presymptomatically is thus indicated. In response to this need the Genetic Services Division of the Department of National Health and Population Development has instituted a screening programme to this end[27].

Many other examples illustrate the need to identify at risk individuals presymptomatically with a view to prevent the manifestation of an adverse reaction to whatever the precipitating environmental agent may be.

Basic principles in ecogenetics

From the above, several principles may be defined which pertain to the nature of ecogenetic reactions and manifestations, namely:

- A specific genotype must prevail which predisposes the sensitivity or susceptibility to an environmental agent and resultant ecogenetic manifestation.

Inter individual differences in susceptibility can be related to a single gene (monogenic) or more commonly to several genes, ie multifactorial component.

- The individuals at risk, in ecogenetic terms, implies a presymptomatic condition which only becomes acute when certain environmental conditions prevail. The classic apparent genetic disorders such as Huntington disease or haemophilia are generally not implied.

One in 300 Afrikaners has the gene for variegate porphyria –100x more than in any other population

- The environmental agents eliciting a detrimental effect may be naturally occurring substances or factors such as sunlight, nutritional compounds, infective and other organisms, plant or animal substances, certain elements or other agents and factors, or the agents may be man-made compounds or environmental conditions eg gases, drugs and chemicals.
- The threshold level at which the ecogenetic manifestation starts, is much lower than that level at which the environmental agent becomes detrimental to unaffected individuals.
- The type of ecogenetic manifestation or response to a particular environmental agent may be evident in the form of a specific disease entity, mutation, teratogenic, carcinogenic, pharmacogenetic or other ecogenetic effect.
- Manifestation of the response may present at birth, post-natally, post-pubertally, or even in the following generation.
- Manifestation of ecogenetic responses can be avoided in most cases, hence the need for presymptomatic identification.
- The environmental agents precipitating ecogenetic responses are still unknown in many cases.

Extending the concept of pharmacogenetics to include genetically determined differences among individuals in their susceptibility to the actions of chemical, physical and biological agents in the environment implies far-reaching implications. Considering that these differential "reactions" not only pertain to drugs, but food, pollutants, stimu-

lants, physical agents, climatic conditions and even auto-immune and infectious disorders, one cannot avoid realising that the implications are also of public health concern. Screening individuals at risk, especially at the pre-symptomatic stage, is indicated. This would express the need to protect these individuals from an unnecessary risk in an environment to which the general population is tolerant. Such a procedure would enable industry or even health authorities to avoid liability for undesired effects of certain environments by preventing persons at highest risk to be exposed to the risk factor(s). With all the best intentions one should not overlook the potential ethical and legal implications. The implemention of larger programmes to detect high risk individuals should for economic reasons, be based on a selected population basis since it could evolve into a political issue.

Before embarking on a national health programme of this nature many answers will first have to be sought before adopting a general policy. The general principles of ecogenetics will have to be researched for a particular population in a particular environment. No population can be assumed to be susceptible for an environmental agent in any degree unless that particular frequency has been assessed scientifically. Genetic knowledge of populations and their subgroup composition could add to the desirability of introducing screening tests. In all cases the biochemical mechanism of the "reaction" to the detrimental agent should be established for a population or sub-population in a particular environment. The metabolism and metabolic effects of many environmental agents, be it

Screening individuals at risk is indicated; it would protect them from unnecessary reactions to which the general population is tolerant

foodstuffs, industrial wastes or other potentially harmful factors, is not known in most cases. Drugs used for medical reasons can easily be influenced by chemicals in man's environment. How far should one insist on screening and detecting relatives of an at-risk individual, and who is to accept responsibility if pre-symptomatic detection is not carried out, if indicated? These questions and many others caution us to embark over enthusiastically on programmes to help and to "protect" the high risk individuals. Perhaps a first step in this direction can be for general practitioners to compile family pedigrees for the patients in their practice. Much has been learned in medicine by following families through generations. GPs are ideally placed to do this.

References

1. Harris H. Enzyme and protein polymorphism in human populations. *Brit Med Bull* 1969; **25:** 5.
2. Stanbury J B, Wyngaarden J B, Fredrickson D S, Goldstein J L and Brown M S. The metabolic basis of inherited disease. (5th Ed) McGraw-Hill 1983.
3. Vogel F. Moderne Probleme der Humangenetik. *Ergeb Inn Med Kinderheilk* 1959; **12:** 52-125.
4. WHO Report. Pharmacogenetics. *WHO Technical Report Series No 524*, 1973.
5. Evans D A P, Clarke C A. Pharmacogenetics. *Brit Med Bull* 1961; **17:** 234-40.
6. Brewer G J. Human ecology an expanding role for the human geneticist. *Am J Hum Genet* 1971; **23:** 92-4.
7. Pauling L, Itano H, Singer S J, Wells I C. Sickle cell anaemia: a molecular disease. *Science* 1949; **110:** 543.
8. Motulsky A G. Drug reactions, enzymes and biochemical genetics. *J Am Med Ass* 1957; **165:** 835-7.
9. Betler E. Glucose-6-Phosphate Dehydrogenase Deficiency. In: The metabolic basis of inherited disease (5th ed). Eds: Stanbury J B, Wyngaarden J B, Fredrickson D S, Goldstein J L, Brown M S. McGraw-Hill, New York 1938.
10. Naik S N, Anderson D E. G-6-PD deficiency and cancer. *Lancet* 1970; **1:** 1185.
11. Shaw C R. Electrophoretic variations in enzymes. *Science* 1965; **149:** 936-43.
12. Motulsky A G. Ecogenetics: genetic variation in susceptibility to environmental agents. Proceedings of the 5th International Congress of Human Genetics. Mexico City, October 1976. *Excerpta Medica*, Amsterdam 1977; 375-85.
13. Harris H, Hopkinson D A. Average heterozygosity per locus in man: an estimate based on the incidence of enzyme polymorphisms. *Ann Hum Genet* 1972; **36:** 9-20.
14. Nei M. Gene duplication and nucleotide substitution in evolution. *Nature* 1969; **221:** 40-2.
15. Lehman H, Ryan E. The familial incidence of low pseudocholin esterase level. *Lancet* 1956; **ii:** 124.
16. Goedde H W, Altland K. Suxamethonium sensitivity. *Ann NY Acad Sci* 1971; **179:** 695-770.
17. Kalm A. G6PD variants. International Titisee Conference. October 1977. *Hum Genet* (Suppl 1) 1978; 37-44.
18. Goedde H, Agarwal P D. Pseudocholinesterase variation. International Titisee Conference. October 1977. *Hum Genet* (Suppl 1) 1978; 45-56.
19. Op't Hof J. Genetic predisposition to environmental health hazards. Proceedings: Man: endangered species. World Environmental Day Conference, Pretoria, 5-7 June 1985.
20. Dean G. The Porphyrias: A story of inheritance and environment (2nd Ed, 1977). Pitman Medical Ltd, 1963.
21. McColl K E L, Moore R. The Porphyrias. An example of pharmacogenetic disease. *Scott Med J* 1981; **24:** 32-40.
22. Meyer U A. Drug sensitivity in hereditary hepatic porphyria. International Titisee Conference, October 1977. *Hum Genet* (Suppl 1) 1978; 71-8.
23. Hitzeroth H W. Ecogenetics: Latest edition to Genetic Services. Perspective in Human Genetics in South Africa, 1980. Department of Health and Welfare, Genetic Services, Pretoria, RSA.
24. Op't Hof J. Bedryfsgenetika. *Rehabilitation in SA* 1984; **28**(4): 112-6.
25. Haldane J B S. Heredity and Politics. N.W. Norton, New York, 1938.
26. Bissport S, Hitzeroth H W, Van den Berg, Van Niekerk L, de Villiers L S, Niehaus C E, Op't Hof J. Die alfa-1-antitripsien polimorfisme as 'n ekogenetiese merker:

Genetiese siftingstoetse en 'n voorkomende mediesgenetiese diens. *Geneeskunde* April 1986; 62-8.
27. Genetic Services, Annual Report 1983-1984. Department of National Health and Population Development, Pretoria, RSA.
28. Wyndham CH. Ischaemic heart disease mortality rates in White South Africans compared with other populations. *S Afr Med J* 1978; **55:** 595-601.
29. Jenkins T, Nicholls E, Gordon E, Mendelsohn D, Seftel HC, Andrew MJA. Familial hypercholesterolaemia - a common genetic disorder in the Afrikaans population. *S Afr Med J* 1980; **57:** 943-7.
30. Seftel HC, Barker SG, Sandler MP, Forman MB, Joffe BJ, Mendelsohn D, Jenkins T, Mienie CJ. A host of hypercholesterolaemic homozygotes in South Africa. *Br Med J* 1980. **281:** 633-6.
31. Motulsky AG. History and current status of pharmacogenetics. In: *Human Genetics:* Proceedings of the 4th International Congress of Human Genetics. Paris. Sept 1971 *Exerpta Medica,* Amsterdam 1972; 381-90.
32. Huygen FJA. Family Medicine. The medical life history of families. Nijmegen Dekker and Van De Vegt 1978.

There will always be individuals who, because of their genetic constitution will not be able to cope in a certain workplace even though the environmental agent would be at a safe level for most others.

Genetic Services

Genetics nurses are available in each health region to assist families who have a need for genetic counselling. These nurses are trained to assist both with the investigation of birth defects and the coordination of assistance to affected families. They may be contacted at any of the following addresses: (Stipulate in correspondence, for attention: *Genetic Nursing Services.*)

Private Bag X19, Bellville 7530. Tel: (021) 97-8151.

PO Box 441, Bloemfontein 9300. Tel: (051) 47-2194.

Private Bag X54318, Durban 4000. Tel: (031) 31-9375, 31-9381.

Private Bag X9067, Pietermaritzburg 3200. Tel: (0331) 4-1901.

PO Box 8623, Johannesburg 2000. Tel: (011) 836-2238, 836-2232.

405 Louis Pasteur Building, Schoeman Street, Pretoria 0002. Tel: (012) 21-8711.

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Private Bag 5023, Kimberley 8300. Tel: (0531) 2-9524.

From the journals

Equity in the distribution of health and welfare services: can we rely on the state to reverse the 'inverse care law?'

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Abstract It has been suggested that the fiscal crises experienced in many industrial nations has been made worse by the drain on the state's economy of an ever-growing welfare state. Proposals to decentralize funding for health and welfare services, and to rely more on local, private, and 'grass roots' services, have been received enthusiastically. The question raised in this paper is whether the shift away from provision by the state will bring about a more or less equitable distribution of resources. The paper considers the spatial distribution of treatment services for two groups of the population who have become largely dependent on the state: namely, the mentally ill and alcoholics. The results suggest that as the federal government withdraws from the provision of services, neither the states nor the localities can be relied on to guarantee a minimum level of services to the truly needy. In the case of alcoholism services there is also some question about whether 'grass-roots' provision would be sufficiently responsive to the distribution of needs.

Ethical issues regarding mixed agency of military physicians

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Abstract Military physicians' obligations to the military may compete with or even override their obligations to patients, especially during combat. Doctor/patient trust may be impaired when the soldier/patient's interests conflict with those of the military and the physician's loyalty is uncertain, and when the military physician treats civilians in occupied territories during mass casualties or, in part, for political gain. When the military physician is asked to perform research which could potentially be utilised for offensive purposes, obligations to the medical profession or to humanity may take precedence over his obligations to the military.